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VOLUME 13
1925

PUBLISHERS
AMERICAN MEDICAL ASSOCIATION
CHICAGO, ILL.

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JANUARY, 1925

PUBLISHED MONTHLY BY AMERICAN MEDICAL ASSOCIATION, 535 NORTH DEARBORN STREET, CHICAGO, ILLINOIS. ANNUAL SUBSCRIPTION, $8.00

Entered as Second-Class Matter, Jan. 7, 1919, at the Postoffice in Chicago, Illinois, Under the Act of March 3, 1879. Acceptance for mailing at special rate of postage provided for in Section 1103, Act of Oct. 3, 1917, authorized Jan. 15, 1919.

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Archives of Neurology and Psychiatry

VOLUME 13 JANUARY, 1925 NUMBER 1

HEREDITARY AND FAMILIAL FACTORS IN THE DEVELOPMENT OF THE PSYCHOSES

ALBERT M. BARRETT, M.D.

ANN ARBOR, MICH.

In considering the individual personality, whether in health or disease, one must recognize the fundamental proposition that persons differ in their reactions to the various forces and experiences they encounter in the environment. These differences are in large part determined by factors inherent in the individual constitution.

One may gain a well formulated conception of what is implied in the connotation of constitution as it pertains to the problems of pathology from the statement of Bauer [1] in his work on "Constitutional Disposition to Disease." In discussing the variability of individual disposition to disease, he states: "This variability rests on the individual and temporal differences of the body states. This, in turn, results from two factors: first, those qualities that are transmitted in the germ plasm or those qualities that are laid down at the moment of fertilization, and, second, the multiform intra- and extra-uterine acquisitions, influences and adaptations of the organism." The first of these factors Bauer designates as constitution and the second as conditioning. Both together determine the disposition to disease. These distinctions have been stated by Kretschmer [2] in much the same way; he defines the constitution as "The totality of all individual characteristics that are attributable to heredity."

The sources of a person's constitution lie in the germ plasm of his ancestors. What turns this from normal to pathologic directions we do not know. From analogies in genetic biology and in pathology it might have come from mutations, from blastophoric disturbances or have become conditioned from hormonal influences of pathologic endocrine relations.

Conceptions of hereditary and familial relations of the psychoses have been broadened and more precisely outlined by the recognition that psychiatric disorders are fundamentally biologic in their interrelations

1. Bauer, J.: Die konstitutionelle Disposition zu inneren Krankheiten, Springer, Berlin, 1921.

2. Kretschmer, Ernst: Körperbau und Charakter, Springer, Berlin, 1921.

and that they link up with qualities and reaction types that are present in normal persons. This makes it possible to bring into the consideration of this question data and correlations from a variety of fields of normal and pathologic psychic qualities, and as has been shown by Kretschmer, a complex interrelationship with somatic and physiologic qualities.

Recognition of inherited or familial factors in disorders of the mind dates from the beginning of medical interest in insanity. It was appreciated that descendants were influenced by transmission of qualities, both normal and abnormal, from their antecedents. The problem of the extent and nature of these hereditary relations has been discussed in an abundant literature dealing with the subject from various aspects, chiefly those of statistical compilations, analytic and interpretative considerations, and more recently from biologic constitutional relationships. Observations and facts have been difficult to interpret and correlate, largely by reason of varying conceptions of the value and limitations of the factors involved in such studies and the continually changing points of view that are inherent in the progressive development of scientific knowledge.

GENERAL HEREDITY

The first question that arises in the consideration of hereditary and familial relations of the psychoses is whether or not there exists any difference in respect to factors of heredity between the psychotic and nonpysychotic person; if so, what differences exist in the quality and relationship of these factors to the individual.

Considerations of this question have usually been based on the comparisons that exist in two groups of statistics that until now represent the most critical information on this aspect of the subject. These are the studies of Koller [3] in 1894, and of Diem [4] in 1905, on the comparative frequency and relation of factors of heredity among two series of persons—one psychotic and the other nonpsychotic.

Koller compared a series of 370 nonpsychotic persons with an equal number of those who were psychotic. As factors commonly regarded as of importance in the heredity of the psychoses, she considered the occurrence of insanity, nervous diseases, apoplexy, alcoholism, senile dementia, abnormal character and suicide, and noted in what relation these factors stood to the individual. It was shown that hereditary taint occurred in 76.8 per cent. of psychotic persons and in

3. Koller, Jenny: Beitrag zur Erblichkeitsstatistik der Geisteskranken im Canton Zürich, Arch. f. Psychiat. **27**:268, 1895.

4. Diem, Otto: Die psycho-neurotische erbliche Belastung der Geistesgesunden und der Geisteskranken, Arch. f. Rass. u. ges. Biol. **2**:215 and 336, 1905.

59 per cent. of those without psychoses. Her conclusions were that hereditary tainting of nonpsychotic persons is far greater than has been generally appreciated; that the most frequent abnormal factors among the antecedents and families of psychotic persons are psychoses and abnormal character. Apoplexy, senile dementia and a large part of the so-called nervous diseases are negligible as taints of heredity of psychotic persons, as they occur in about the same proportions in the two groups, or are even more frequent in the nonpsychotic group.

Diem, in a study of a series of 1,193 nonpsychotic persons, found that 66.9 per cent. of this group were in some way tainted and that only 33.1 per cent. were free from abnormalities of the family. For comparison, he studied a series of 3,515 psychotic patients (Table 1). Here he found a hereditary taint in 77 per cent., or about four fifths of the entire group. This agrees fairly well with Koller's findings and shows that the difference in the total hereditary tainting of psychotic and nonpsychotic patients is not significant, 77 per cent. as against 66.9 per cent. There is, however, a definite difference in the family relationship of the various abnormalities to the individuals of the two groups. While 33 per cent. of the nonpsychotic group are directly tainted from the parents, direct inheritance occurs in from 50 to 57 per cent. of the psychotic group. The tainting from more remote members, i. e., uncles, aunts and grandparents occurs in from 20 to 28 per cent. of psychotic and in 34 per cent. of nonpsychotic persons. There are, however, marked differences in the quality of the inheritance in the two groups. Psychoses occur three times more frequently among psychotic than among nonpsychotic persons. Alcohol and abnormal character are of equal importance, but nervous diseases, apoplexy and senile dementia are only a third as frequent in psychotic as in nonpsychotic patients. The parents and siblings of psychotic persons have almost twice as many factors of heredity as those of nonpsychotic persons. Diem's chief conclusions were:

1. Psychotic patients are in general more heavily tainted with psychoses, alcoholism and character anomalies than nonpsychotic patients. Nonpsychotic patients are more tainted with apoplexy and senile dementia than psychotic patients. The total tainting from all factors is in psychotic persons predominantly direct, in smaller part, more remote. Indirect tainting is in the nonpsychotic much greater than in the psychotic. The siblings of psychotic are more tainted than those of nonpsychotic parents. "The working of a regenerating influence is incontestable, but the fact of the direct heredity is unmistakable."

The outstanding fact from both Koller's and Diem's investigations is that hereditary tainting must be recognized as of fundamental importance in the etiology of the psychoses.

TABLE 1.—*Hereditary Factors in the Psychoses Compiled from Tables of Koller, Diem, Kalb, Snell and Sünner*

	Psychoses	Nervous Diseases	Alcoholism	Apoplexy	Senile Dementia	Abnormal Character	Suicide	Total All Hereditary Factors	Percentage Total Hereditary Factors
1,193 Nonpsychotic (Diem)									
Direct	35	86	138	83	21	75	6	444	33
Atavistic	33	22	74	163	97	57	6	452	29
Collateral	144	75	146	93	25	190	12	685	..
Sibling	82	108	55	19	1	92	7	364	5
Total hereditary	294	291	413	358	144	414	31	1,945	..
Percentage	15.1	14.9	21.3	18.4	7.4	21.3	1.6	100	67
3,515 Psychotic (Koller and Diem)									
Percentage hereditary factors	45.9	5.1	20.9	5.5	1.4	18.8	2.3	...	77 (Diem)
205 General Paralysis (Kalb)									
Direct	10	6	13	17	2	10	3	61	27.3
Atavistic	8	1	8	28	4	1	1	51	....
Collateral	19	8	3	20	1	3	5	59	30.7
Sibling	22	9	7	..	..	10	2	50	9.7
Total hereditary	59	24	31	65	7	24	11	221	..
Percentage	26.7	10.9	14.0	29.4	3.2	10.9	4.9	100	67.7
352 Epilepsy (Snell)									
Direct	21	60	95	19	1	38	3	237	59.09
Atavistic	19	13	16	12	1	9	0	70	16.77
Collateral	45	25	11	1	1	10	9	102	5.4
Sibling	28	44	8	1	..	10	2	93	.....
Total hereditary	113	142	130	33	3	67	14	502	.....
Percentage	22.51	28.28	25.89	6.57	0.59	13.34	2.79	100	81.26
650 Manic-depressive (Sünner)									
Direct	151	136	77	70	18	72	11	535	65.53
Atavistic	60	27	11	51	13	19	5	186	.....
Collateral	128	28	17	6	2	18	18	217	14.76
Sibling	143	75	3	3	0	18	19	261	4.76
Total hereditary	482	266	108	130	33	127	53	1,199	.....
Percentage	43.86	15.1	9.8	11.8	3.0	11.5	4.8	100	84.13

The methods followed in these analyses have been criticized especially by Wagner von Jauregg,[5] but as Rüdin [6] recently commented, "Until we have a series of statistics on the mentally healthy compiled with the modern point of view, we must use those of Koller and Diem, which give in general such plausible results that the truth does not lie far off."

The importance of the direct inheritance in the psychotic person is generally recognized in all available statistical compilations. The question arises in relation to hereditary factors in the psychoses whether the male or female antecedent is more likely to transmit the taint. It has been generally found that hereditary tainting is more frequent in the families of female patients than male. In Diem's tables, hereditary factors occur 5.5 per cent. more frequently among females. In a series of 752 instances, Mott [7] found that when two of a family were psychotic there was much greater incidence of transmission from parents to offspring through the female side than through the male side.

TABLE 2.—*Parental Hereditary (Mott)*

Relationship	Instances	Male	Female
Father and son	44	88	..
Mother and son	51	51	51
Father and daughter	58	58	58
Mother and daughter	104	..	208

In percentage relations, the father transmits to the offspring in 39.3 and the mother in 60.7 per cent. Mott comments that these figures agree closely with the statistics of Gowers,[8] who found in investigating the question of insanity of the parent and epilepsy of the descendants that the father was insane in 37 per cent. and the mother in 63 per cent. of instances. Myerson,[9] in a somewhat larger series, found similar relations. The transmission was from the father in 43.7 per cent. of 414 instances and from the mother in 56.2 per cent. Mott [7] found that the mother transmits to the daughter nearly twice as often as does the father. Myerson [9] concludes that insane mothers tend to have insane daughters more than insane sons, but the father-son relationship is only

5. Von Jauregg, Wagner: Einiges über erbliche Belastung, Wien. klin. Wchnschr., No. 1, 1906.

6. Rüdin, Ernst: Neuere psychiatrischegenealogische Untersuchungen nach der Diem-Kollerschen Belastungsberechnung, Zentralbl. f. d. ges. Neurol. u. Psychiat. **29**:172, 1922.

7. Mott, F. W.: Heredity and Insanity, Eugenics Rev. **2**:257, 1910-1911.

8. Gowers, W. R.: Epilepsy and Other Chronic Convulsive Diseases, New York, William Wood and Company, 1885.

9. Myerson, A.: Psychiatric Family Studies, Am. J. Insan. **73**:355, 1916-1917.

slightly less common than father to daughter. In agreement with this, Tigges [10] comments that daughters with direct maternal heredity are more frequently found to be insane than are daughters in the direct paternal heredity.

In forming any conclusions regarding the differences in potency of males or females in transmitting abnormalities, one must take into account the completeness of information available in the histories analyzed. Diem is inclined to regard these differences as statistical artefacts, possibly explainable by the fact that in hospital statistics fuller information is usually obtained in regard to female than male patients. Fundamentally, this question is involved in the problem of sex linked qualities, and information on this point can better be accumulated from the study of specific types of psychoses than from data that have been compiled using insanity as a unit character. No available data indicate definitely that any type of psychosis is sex linked.

Similar or Dissimilar Heredity.—A fundamental question of the mechanism of heredity in the psychoses is whether or not the psychosis of the descendant is similar or dissimilar to that of the antecedent, or other members of a family. This question is complex in its relations. Instances of dissimilarities are common, but the occurrence of different types of psychoses in the parents or families of a psychotic person does not disprove similarity of inheritance. Much evidence has been gained from recent studies of special families by biogenetic methods that heredity in at least some of the psychoses is not general but specific. "Polymorphous heredity is today not contradicted nor proven. Its occurrence from a Mendelian viewpoint may be possible."—*Rüdin.*[11] This does not mean that a disease may create a new type. It seems probable that disease phenotypes are determined by unit characters that maintain their independence, and that each phenotype distributes its unit qualities to descendants according to mendelian rules. The product may be a pure constitution for a type disease or one that is complex from the interacting of several unit qualities, e. g., schizophrenic cyclothymia, schizoid-alcoholic, schizophrenic epilepsy, cycloid schizophrenia, etc. Such intermingling of qualities of different psychoses seems to correlate with specific somatic constitutional characteristics. Kretschmer [2] and Hoffman [12] have considered these as alloys of constitutional qualities.

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10. Tigges, W.: Untersuchungen über die erbliche Belasteten Geisteskranken, Allg. Ztschr. f. Psychiat. **63**:1 1907.

11. Rüdin, Ernst: Zur Vererbung und Neuenstehung der Dementia praecox, Monog. aus. d. gesamtgeb. der Neurol. u. Psychiat., No. 12, Berlin, Springer, 1916.

12. Hoffman, Herman: Die Nachkommenschaft bei endogenen Psychosen, Monog. aus. d. gesamtgeb. der Neurol. u. Psychiat., No. 26, Berlin, Springer, 1921.

One also is familiar with atypical manifestations in recurrent attacks of psychoses. Certain attacks may be of manic or depressive type, while others may be schizophrenic. To such phenomena, Hoffman has applied the term "change of dominance." Both of these variants from typical relations are referable to the determining influence of specific factors in the antecedents, transmitted to the descendants. They are fundamental conceptions in the problems of the heredity of the psychoses and bear intimately on questions of similarity and dissimilarity of inheritance. Inheritance in the endogenous psychoses tends to show a predominance of specific or closely correlated clinical types in a family stock, e. g., schizophrenic and cyclothymic families, and that inheritance in these two great groups is of similar qualities.

Rosanoff,[13] in his studies of this question, presents much material showing the intermingling of dissimilar diseases in families, and concludes that "an hereditary relationship exists between various neuropathic conditions which are clinically sharply distinguished from one another," and that "these neuropathic conditions possess in common the property of behaving as recessive traits in the mendelian sense in relation to the normal conditions. Myerson,[8] in his contribution, presents a variety of instances of dissimilar heredity, but also cites evidence that certain clinical types stand in some sort of correlation with other clinical forms, e. g., "paranoid conditions in the ancestors tend to dementia praecox in descendants." "Manic-depressive psychoses are followed by dementia praecox." In support of similar heredity, he comments: "I am certain that the clearly uncomplicated cases of manic-depressive insanity are followed by manic-depressive insanity," and "dementia praecox breeds true for it is followed in the great majority of those cases where insanity occurs in the next generation by dementia praecox." Mott [7] concludes in a study of general heredity that "a periodically insane son or daughter is more apt to be associated with a periodically insane brother or sister than with one differently affected." Mott further comments that in delusional insanity the tendency for the affection to run in families is strongly marked, and correlation between members of the same cofraternity is more marked than between parents and offspring. In cases of primary dementia of adolescence, there is a strong correlation between members of the same cofraternity, also a decided tendency for brothers and sisters of imbeciles to be imbeciles.

In the greater number of contributions dealing with this aspect of heredity, undoubted instances of family interrelations of clinically differentiable mental disorders are presented, but in most of these there is

13. Rosanoff, A. J.: Dissimilar Heredity in Mental Diseases, Am. J. Insan. **70**:1, 1913.

also a clear recognition that correlations exist among specific clinical types (Jolly,[14] Luther,[15] Krueger[16]).

One gains a somewhat more detailed insight into the question of similar or dissimilar heredity in the psychoses from a number of recent studies in which the problem has been investigated by applying modern biogenetic methods to the study of specific types of disorders as they occur in families (Rüdin,[11] Hoffman,[12] Kahn,[17] Wimmer,[18] Minkowski[19]).

In studying the familial occurrence of schizophrenia, Rüdin[6] found that in a series of 721 schizophrenic persons seventy-nine had siblings who were not schizophrenic. Of a series of 735 siblings, one of whom had dementia praecox, only fifty-nine probably came from parents with dementia praecox. There were 130 parents who had a psychosis that was not dementia praecox. In less than a third, there was a similar heredity. Among eighty-one descendants of twenty persons with old cases of dementia praecox, not more than three had dementia praecox. Among these descendants there were such disorders as epilepsy, imbecility, alcoholic psychosis and psychopathic inferiority. Facts, such as these, Rüdin believes, do not show that when dementia praecox is present in parents or siblings a new psychosis will be dementia praecox.

Hoffman[12] found among the children of manic-depressive parents, besides those who had manic-depressive qualities, instances of schizophrenia, feeblemindedness and epilepsy.

Such observations as these of Rüdin and Hoffman tend to show that heredity may be dissimilar. There is, however, evidence that supports the view of similar heredity and that in spite of dissimilar phenotypes in a family strain dissimilar specific factors do not fuse or unite to produce a new phenotype. This is shown in the recent studies dealing with the inheritance of constitutional types and familial relations of schizoid and cycloid qualities, notably those by Rüdin,[11] Kretchmer,[2] Binzwanger,[20]

14. Jolly, P.: Die Heredität der Psychosen, Arch. f. Psychiat. **52**:311 and 492, 1913.

15. Luther, A.: Erblichkeitsbeziehungen der Psychosen, Ztschr. f. d. ges. Neurol. u. Psychiat. **25**:12, 1914.

16. Krueger: Zur Frage nach der nosologischen Stellung der "Paraphrenien," Ztschr. f. d. ges. Neurol. u. Psychiat. **28**:456, 1914.

17. Kahn, Eugen: Schizoid und Schizophrenie im Erbgang, Monog. aus d. gesamtgeb. der Neurol. u. Psychiat., No. 36, Berlin, Springer, 1923.

18. Wimmer, Augusta: Sur la transmission héréditaire des maladies mentales, l'Encéphale **17**:129, 1922.

19. Minkowski, Franziska and Eugen: Probleme der Vererbung von Geisteskrankheiten auf Grund von psychiatrischen und genealogischen Untersuchungen an zwei Familien, Schweiz. Arch. f. Neurol. u. Psychiat. **12**:47, 1923.

20. Binzwanger, K.: Ueber schizoidie alkoholiker, Ztschr. f. d. ges. Neurol. u. Psychiat. **60**:127, 1920.

Kahn,[17] Hoffman [12] and others. All of these tend to show that specific qualities behaving as genes maintained their purity in hereditary transmission. They may combine to produce complex combinations in a phenotype, but schizoid as a genotype does not become cycloid. If a dissimilar type occurs in a family strain, it has its source in a specific gen that has been present previously in the germ plasm of some ancestor. It would seem that one must conclude from the data now available that various clinical types of psychoses may intermingle in families. In this respect, dissimilar heredity may occur. There is also much evidence to justify the conclusion that the anlage of a specific clinical type of disorder is determined by factors received from like or closely correlated anlagen, and in this respect heredity is similar. It also seems probable that various specific factors may, while maintaining their primary discreteness, combine to produce complex phenotypes. In certain families, specific clinical types tend to predominate.

Anticipation or Antedating.—The conclusion seems justified from the literature that psychoses of descendants tend to develop at an earlier age than in their antecedents. Rosanoff,[13] from a study of this question on a large material concluded: "After all probable error has been discounted the fact remains that in the majority of cases in which a difference is observed the gravity of the neuropathic manifestations is less and the age of onset is higher in parents than in their offspring." Mott,[7] in a similar study, found that there is an anticipation factor in the development of psychoses of descendants, and that the great bulk of offspring are affected at earlier age periods than their parents. Myerson,[9] from an analysis of material from Taunton and a review of the literature, came to similar conclusions. The most notable opposing view to these conclusions is that of Jolly,[14] who comments that he finds no progressive degeneration in families and that a disease is not more severe in the children than in the parents.

A consideration of this question in relation to specific clinical groups has been made by Rüdin [11] and Hoffman.[12] In schizophrenia, Rüdin found that older siblings tend to develop the disease at a later age than their younger siblings. In seventy-two cases, the earliest born developed dementia praecox at an average age of 25.8 years. In seventy-two cases of the next born, the average age of development was 24.6 years. Hoffman found that manic-depressive psychoses of descendants began at an earlier age than in their parents, and that when cyclothymic anlagen were present in both parents the antedating was greater.

Mendelian Relations.—A new orientation in psychiatry came with the application of mendelian theories to the investigations of problems of heredity in relation with the psychoses. Since the contribution of God-

dard in 1911 [21] dealing with mental defectiveness, of Davenport in 1911 [22] in studies of epilepsy and the formulations by Rüdin [23] in the same year of mendelian theories as they might be applied to psychiatric family investigations, there has accumulated a considerable literature bearing on various relations of this question. The more important of these dealing with specific questions are by Rüdin and his associates in the *Deutsche Forschungsanstalt für Psychiatrie in Munich,* and have appeared within the past seven years. These contributions present facts drawn from the studies of interesting family groups rather than large statistical surveys. Many of the observations presented can be accepted as fundamental for future conceptions, while others offer interesting suggestions.

It is generally agreed that hereditary factors are most prominent in the endogenous psychoses. It seems to have been convincingly shown that they are of fundamental importance in the etiology of manic-depressive psychoses, schizophrenia, mental defectiveness, constitutional psychopathic inferiority, epilepsy and Huntington's chorea. There is some evidence that they play a part in the occurrence of paranoid states and arteriosclerosis, and that they may be factors to be considered in senile dementia and symptomatic mental disorders has not been excluded.

HEREDITY IN MANIC-DEPRESSIVE PSYCHOSES

Clinical experience has shown that the conception of this disorder cannot be limited alone to episodic attacks of excitement or depression, and that one must include with these a considerable range of abnormalities of hyperaffective and hypo-affective relations and variations of temperament that shade over into qualities of constitution that are difficult to differentiate from those of the average or normal person.

This broadened conception of the disorder is connoted in the term "the cyclothymic constitution." A fundamental factor in this type of constitution is that quality that has recently become familiar to us in the designation, cycloid. Kretschmer [2] has formulated the cycloid constitution as one that has in affective qualities variations between elevated and depressed moods, a psychic tempo that shows in a temperament varying between activity and quietude and a psychomotility that is in harmonious relations with the stimulus. These qualities are basic characteristics of the frank phases of mania or depression and are also often

21. Goddard, Henry H.: Heredity of Feeblemindedness, Bull. No. 1, Eugenics Record Office, Coldspring Harbor, N. Y., 1911.

22. Davenport, C. B., and Weeks, F.: A First Study of Inheritance in Epilepsy, Bull. No. 4, Eugenics Record Office, Coldspring Harbor, N. Y., 1911.

23. Rüdin, Ernst: Einige Wege und Ziele der Familienforschung, Ztschr. f. d. ges. Neurol. u. Psychiat. **7**:217-284, 1911.

manifest in the prepsychotic and interval periods of the disorder. Such qualities may also characterize persons who, while never manifesting definite psychotic attacks, show in their life course cycloid qualities to a degree that distinguishes them as cycloid psychopaths. Cycloid qualities may have a determining influence in shaping the symptoms or type of course of other psychoses not dominantly manic-depressive, and thus produce complex clinical manifestations, such as cycloid forms of schizophrenia, general paralysis and epilepsy. There is much evidence that cycloid qualities are transmissible and intermingle among families some of whose members are frank cases of manic-depressive psychoses.

General Relations.—The percentage in which heredity plays a part in cyclothymia has been variously given, depending largely on the completeness of information and the point of view of the compiler. In general, it has been found that hereditary factors are far more frequent in this disorder than in any other psychosis. Kraepelin [24] found hereditary tainting in 80 per cent. of cases in the Heidelberg clinic, and he states that a pathologic predisposition is the most important factor in the causation of manic-depressive insanity.

The best available data dealing with general hereditary relations in this disorder are to be found in the contribution of Sünner.[25]. In this he considers 650 cases of manic-depressive psychoses from the Munich clinic, and analyzes these in relation to the statistics of Koller and Diem (Table 1). He found that some sort of hereditary tainting existed in 84.13 per cent. of the cases of manic-depressive psychoses. This was much higher than was noted among nonpsychotic patients, namely, 66.9 per cent., or among psychotic patients in general, namely, 77 per cent. The most frequent tainting factors were psychoses among the antecedents. These were noted in 43.86 per cent., which about equals the percentage among psychotic patients in general, namely, 45.9 per cent. Other factors occur as follows: nervous diseases, 15.1 per cent.; apoplexy, 11.8 per cent.; alcoholism, 9.8 per cent.; abnormal character, 11.5 per cent.; suicide, 4.8 per cent.

The parents of persons with manic-depressive cases have some kind of psychoses in 12.5 per cent. of instances, which is a little less than has been found among the general average of psychotic persons, namely, 15.5. This is seven times more than among the parents of the nonpsychotic. Apoplexy occurs in 5 per cent. and suicide in 1 per cent. of the parents. The siblings show abnormalities in 11 per cent., while among nonpsychotic patients only about 3 per cent. of the siblings are abnormal.

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24. Kraepelin, E.: Psychiatrie, Ed. 8, Leipsic, Aug. Barth, 1909.

25. Sünner, Paul: Die psychoneurotische erbliche Belastung bei dem manisch-depressiven Irresein aufgrund der Diem-Kollerschen Belastungsberechnung, Ztschr. f. d. ges. Neurol. u. Psychiat. **77**:453, 1922.

Siblings of patients with manic-depressive psychosis commit suicide more frequently than those of other psychotic patients.

The conclusion seems warranted that of all types of psychoses so far investigated, the manic-depressive most frequently shows hereditary tainting. The tainting is predominantly with psychoses. The transmission of the taint is more frequently in a direct line.

Anteposition.—There seem to be few data that allow any definite conclusions on this point. Hoffman [12] found in a small amount of material that the children from a mating of parents one of whom was manic-depressive and the other free from this disorder, the average age of the patient was 36.8 and of the descendant 32.7 years. If both parents were manic-depressive, the average age of onset in parents and children was 48.2 and 28.4, respectively. It would thus seem that there was a suggestion that antedating occurs.

Mendelian Relations.—Data from the study of families having manic-depressive psychoses among their members show that there is nothing to indicate that mendelian theories are not applicable to their analysis. The majority of evidence tends to indicate that the transmitted factor behaves as a dominant characteristic. This is supported by the observation that manic-depressive psychoses in children of parents with manic-depressive psychoses occur in a higher percentage than does schizophrenia in the children of schizophrenic parents. The proportion of these is 31.4, which does not agree with the expectation of a recessive factor. Dominance is also indicated in the occasional direct inheritance of the disease through three or four generations. There are, however, families that seem to show hereditary relations suggesting a recessive behavior. Rosanoff [13] presents a considerable number of instances that seem to differ from what would be expected were the course that of a dominant character. He proceeds from the assumption that if manic-depressive insanity were dominant over normal, then no cases of this disorder would result from the mating of two normal parents. In an analysis of twenty-eight critically selected cases of manic-depressive psychoses, he found twelve cases from matings of two normal parents. He concludes from this that normal mentality is apparently dominant in relation to manic-depressive insanity and that the assumption of the contrary is not supported by his material.

It is impossible without a personal acquaintance with the material discussed in such a study as that of Rosanoff to agree or disagree with his conclusions. It is obvious that if mendelian relations hold in the heredity of manic-depressive insanity, the germ plasm of one or both of these so-called normal parents contained a latent manic-depressive anlage, although apparently not outwardly manifest. It would be of interest to know whether or not on careful analysis a cycloid quality

might have been shown in their constitution or temperament. One would also have to consider the possibilities of the development of manic-depressive abnormalities in the parents at a later age.

Were the trait recessive, one would expect that about 25 per cent. of the children of parents with manic-depressive psychoses would have a manic-depressive psychosis. Hoffman found among 124 cases of manic-depressive parents that if one narrowed the conception of the disorder so as to include only circular or frank manic or depressive attacks, the proportion realized in the number of children who were manic-depressive would be 31.4. If one includes in the disorder the broad manifestations of the cyclothymic constitution, the proportion is 60 per cent., which is far from the expectation for a recessive type.

The question of the mendelian relations in this disorder is at this time far from solved. Hoffman[12] presents a theory to explain the hereditary mechanisms of cyclothymia that is of interest at this time in that it fits in with current thought regarding the interrelations of constitution and temperament and endocrine pathology. He suggests that there may be two hormones that are antagonistic, one accelerating and one inhibiting in its influence. Should a disturbance occur in the equilibrium of these, this, as it passes beyond a certain value, would bring the affective apparatus into a harmonizing mood. One might thus differentiate two fundamental disturbances whose action brings about the manic-depressive psychosis. One of these, perhaps a lability of the affective apparatus, may be the basic factor in the cyclothymic anlage. This in inheritance follows a dominant course. A manic-depressive psychosis may occur if there is a disturbance of internal secretion of a certain kind which may be caused by different etiologic components. This may be determined by an abnormality of constitution of the different internal secretory glands, which perhaps may be due to hereditary influences coming from the nonpsychotic parent.

The observation that females predominate over males in manic-depressive psychoses has suggested that the anlage might in some way be sex linked. Hoffman, in a study of this question, found that this is not supported by the facts so far known. Were the anlage one of sex linked recessive type, then one would not expect daughters with manic-depressive psychoses from normal parents, or from the mating of a normal man and a woman with manic-depressive psychosis, one would expect only diseased sons, while the daughters would be normal. Were the relationship one of a sex linked dominant type, the mating of two parents with manic-depressive psychoses would give no normal daughters. If the father had manic-depressive psychosis and the mother were normal, one would expect daughters with manic-depressive

psychoses but normal sons. In his material, Hoffman found instances that did not agree with these expectations, and concluded that the transmission was one that could not be regarded as sex linked.

HEREDITY IN SCHIZOPHRENIA

There is an increasing appreciation that heredity plays an important rôle in the etiology of schizophrenia. Studies of the families in which schizophrenia occurs suggest agreement with mendelian theories. Data on this subject are to be found in statistical surveys embodied in hospital reports, in a number of reports dealing with general hereditary relations of the disease and in several recent contributions with a modern biogenetic point of view and method, notably those of Medow,[26] Berze,[27] Rüdin,[11] Kahn,[17] Hoffman,[12] Kretschmer,[2] Bleuler[28] and Heise.[29] It is variously stated that hereditary taint of some sort is to be found in from 50 to 90 per cent. of cases of dementia praecox. Kraepelin,[24] in a study of 1,054 cases, found that hereditary abnormalities occurred in 53.8 per cent. of the families. The heredity was direct in 33.7 per cent. Among the families of dementia-praecox patients, one finds not only instances of dementia praecox, but a high percentage of other psychoses and psychopathic conditions. While this suggests a polymorphous heredity, Rüdin[11] comments that "the assumption of a polymorphous heredity is neither contradicted nor proven. Its occurrence on the ground of mendelian views may well be possible." In his series of 721 patients with dementia praecox, there were not only forty siblings with dementia praecox, but seventy-nine siblings who had other psychoses. Every fourth or fifth parent of a patient with dementia praecox had a mental or nervous disorder of some kind. Of 701 parental pairs, 229 had alcoholism or some type of psychosis in one parent. As the psychoses found in parents or siblings are in part different, the present situation seems to be that the psychoses of the parent and dementia praecox and other psychoses in the children are products of complicated splitting of hereditary processes analogous to what is known in plants and animals. The facts do not show that when a parent or sibling has dementia praecox if a new psychosis developed, it would be dementia praecox.

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26. Medow, W.: Zur Erblichkeitsfrage in der Psychiatrie, Ztschr. f. d. ges. Neurol. u. Psychiat. **26**:491, 1914.

27. Berze, J.: Die hereditären Beziehungen der Dementia Praecox, Leipsic, 1919.

28. Bleuler, E.: Mendelismus bei Psychosen, Schweiz. Arch. f. Neurol. u. Psychiat. **1**:19, 1917.

29. Heise, H.: Der Erbgang der Schizophrenie in der Familie D. und ihren Seitenlinien, Ztschr. f. d. ges. Neurol. u. Psychiat. **64**:229, 1921.

Rüdin found in 735 siblings series with at least one case of dementia praecox that only in less than a third could one speak of a similar heredity. In about a third, the hereditary factors were functional disorders and about a third were of an organic type. Among descendants of patients with dementia praecox, there are found a variety of psychoses other than dementia praecox. There are, however, observations that seem to show that specific hereditary factors are concerned in the production of dementia praecox.

Mendelian Relations.—Investigation of families in which dementia praecox occurs seems to show that mendelian principles are applicable to their analysis. A number of studies, notably those of Rüdin, Kahn and Hoffman, indicate that the dementia praecox anlage is transmitted as a recessive. Rüdin found in a study of 701 siblings series of patients with dementia praecox that the proportion of dementia praecox among these was 4.48 per cent. and that other psychoses occurred in 4.12 per cent. While this suggests a recessive rather than dominant course, it does not agree with the expectation of a simple mendelian character. It suggests more that there is a dihybrid mode of transmission in which two characters are active. He found that dementia praecox occurred more frequently from a mating in which one parent had dementia praecox or if one parent had a psychosis other than dementia praecox than if both parents were free from dementia praecox. It was also more frequent when one or both parents were alcoholic or when one parent was psychotic and the other alcoholic. In instances in which neither parent had a psychosis or was alcoholic, but a remote ancestor had dementia praecox, it was found that dementia praecox occurred more frequently among descendants than when the ancestral line was free from dementia praecox. Such observations tend to indicate that the occurrence of other types of psychoses in the parents and siblings of patients with dementia praecox is not in accidental relation with dementia praecox, but is in some way interrelated with the heredity of the disease.

In support of a recessive as against a dominant course, Rüdin brings forward the following facts: 1. Dementia praecox is rarely observed among children from two parents with dementia praecox; among the children of twenty matings of persons with dementia praecox, there were only two or three descendants who had the same disease. Were the anlage transmitted in a dominant mode, one would expect either all or half of the children to have cases of dementia praecox. 2. Observations of the transmission of dementia praecox through two or more generations are extremely rare. 3. If the course were that of the transmission of a dominant character, it would be possible to state that if a person was once free from the disease, he would never transmit

dementia praecox. Clinical experience shows that this does not hold. 4. The most frequent finding is dementia praecox in children of parents who do not have dementia praecox.

The conclusions from his observations on hereditary relations are that it seems essential that hereditary pathologic factors must act from both parental sides. The psychotic parents of patients with dementia praecox have, more than a healthy parent coming from a healthy strain, a germ plasm out of which alone dementia praecox cannot develop, but through the qualities carried in the germ plasm of the mate may produce the anlage out of which dementia praecox may develop.

Investigations do not tend to show that the transmission is in any way sex limited.

Anteposition.—Rüdin found that the older siblings tended to develop dementia praecox at a later age than the younger. In seventy-two cases those of earlier birth developed the disease at an average age of 25.8 years, while in seventy-two of the next born the average age of onset was 24.6. In fifty cases in which a parent and his child had dementia praecox, the average age of onset in the parent was 36.7 and in the child 24.25 years.

The solution of this question involves a variety of factors that have not always been taken into account, such as the uncertainty of knowing just when dementia praecox begins and the fact that the nature of the disease prevents the majority of patients from becoming parents. Rüdin is not convinced, in spite of the seeming corroborations of antedating, that a clear proof for this has yet been given.

SCHIZOID CONDITIONS AND SCHIZOPHRENIA

Clinical experience shows that in the families of patients with dementia praecox there are frequently persons who have mental peculiarities that are observed in prepsychotic and psychotic phases of dementia praecox. These abnormalities have been designated as schizoid qualities, and persons in which these are of marked degree have come to be classed as schizoid psychopaths. Schizoid and cycloid qualities seem to be specific and fundamental in determining the type of symptoms in the large groups of schizothymia and cyclothymia. In their relations, they have a far wider application than to disease states alone. They are, as Kretschmer [2] states, not synonymous with disease or health, but are inclusive designations for large general biologic types that distinguish temperaments and reaction qualities that are present among average healthy persons.

Kretschmer has characterized the schizoid temperament as having in the affective field a psychesthetic quality varying between the hyper-

esthetic and the anesthetic. In psychic tempo, the reactions correspond to a springy type of temperament curve. In psychomotility, the reactions are inadequate to the stimulus.

Problems of the mechanisms of inheritance of schizophrenia seem to stand in intimate relation with the concept of schizoid qualities and their biologic relation with schizophrenia. If heredity has the important part indicated in schizophrenia, then one must expect that there are other schizophrenic disorders in the families having this disease. The phenotype schizophrenia must always stand in relation with separate

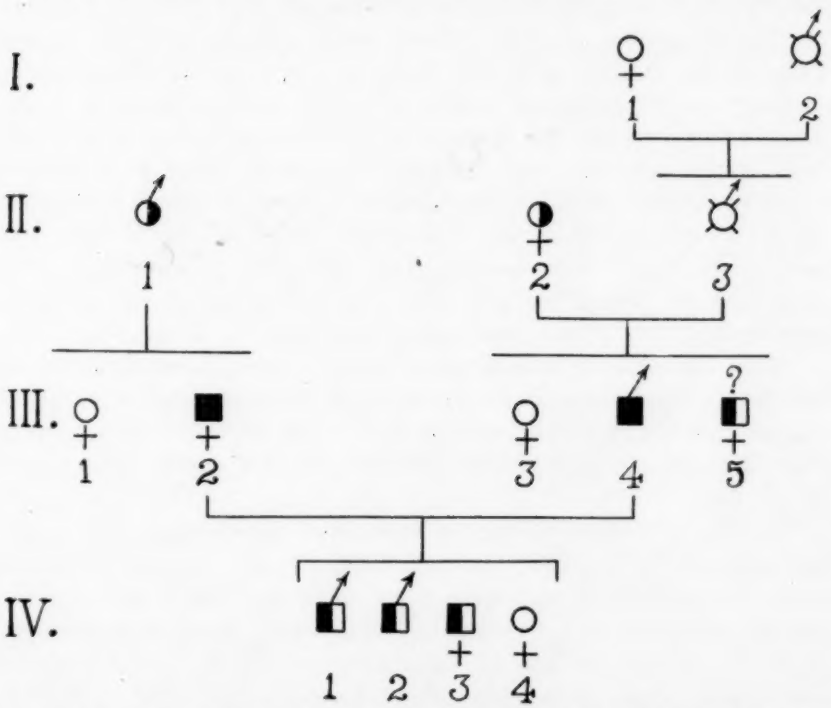

Chart 1.—Schizoid conditions and schizophrenia (Kahn-Wienz family). The circles that are half white and half black indicate psychopathic persons; the white circles with projections, alcoholic persons; the squares that are half black and half white, persons with schizoid conditions; the black squares, persons with schizophrenia.

genotypes. Kahn [17] suggests that there are two outstanding components in schizophrenia—one, the peculiar mentality of the schizophrenic person, which is never absent; and the other, the characteristic schizophrenic type of deterioration, which is scarcely ever missed. The former he identifies with schizoid qualities and the latter as the schizophrenic process. His observations seem to indicate that schizoid qualities follow a dominant hereditary course, while the anlage to the schizophrenic

process is recessive. For the occurrence of schizophrenia, there must be present in addition to the schizophrenic process anlage the dominant schizoid anlage. The question is left open as to whether these two genic factors are simple or complex and whether perhaps still other factors occasionally complicate the hereditary structure of schizophrenia. These genetic interrelations are shown in Chart 1 (Kahn). In the second generation, there were two persons of schizoid quality. In the third, there were two who had schizophrenia and one who was probably schizoid. In the fourth generation from the mating of two schizophrenic parents, there occurred three schizoid descendants.

The recognition of an hereditary relation of the schizoid temperament has led to investigation of its interaction with other factors in the shaping of the symptom manifestations of other psychoses. Binzwanger [20] has studied the relation of the schizoid type to certain alcoholic mental disorders, and Hoffman [12] has investigated its relation to cyclothymic conditions. Such interaction produces complicated phenotypes that clinically show the contrasting symptoms coming from what seem to be specific determiners. The facts seem to show that where these complex phenotypes occur, one can find, in the parents or family, persons who show disorders of contrasting type.

Such interaction is illustrated in Chart 2. This is one of Hoffman's families in which some of the members are schizoid, others cyclothymic and one has a case of dementia praecox. The disorders of two others showed in their course clinical symptoms in part schizoid and in part cyclothymic.

A study of certain cases of melancholia of the involution period suggested to Hoffman that the torpid, unrecoverable melancholia of the involution period or presenium, that shows nihilistic delusions and stereotyped reactions, has certain hereditary relationships with dementia praecox, and that perhaps this has its explanation in the fact that the germ plasm carries an inherited schizophrenic factor.

Kretschmer [2] has shown that the type of body structure in schizothymia is predominantly of an asthenic, athletic or dysplastic type, and in cyclothymia, of a thickset constitutional type that he designates as pyknic ("pyknisch"). In inheritance, these body types maintain a close correlation with schizothymic and cyclothymic qualities of temperament and character. They have not only their correlations in disease, but also in the temperament and character of healthy persons.

HEREDITY IN PARANOID PSYCHOSES

Any investigation of this subject encounters difficulties owing to the lack of sharp differentiation between paranoid types of reaction and schizophrenia in its wider conception. There is little usable information

bearing on this question. Some comments in the literature (Myerson,[9] Rosanoff [13]) seem to show that paranoid qualities of ancestors seem to stand in relation with dementia praecox of descendants. Hoffman [12] states in a study of a small but critically chosen material that the schizophrenic constitution is closely related to the paraphrenic and that paraphrenia usually develops from a schizophrenic constitution.

HEREDITY IN TRUE EPILEPSY

Casual observations and statistical surveys have shown that the families in which epilepsy occurs show a high frequency of hereditary

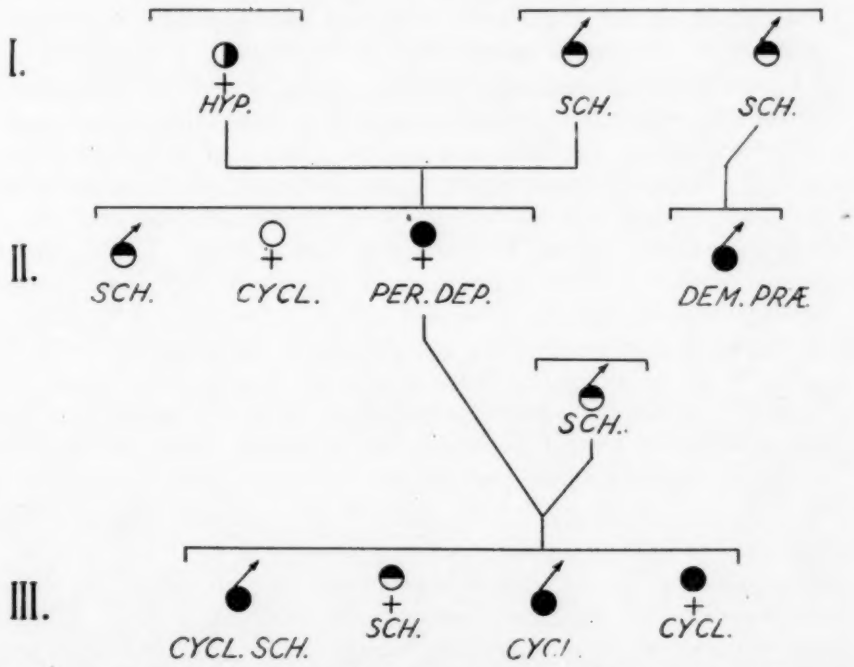

Chart 2.—Cyclothymia and schizoid conditions (Hoffman). *Cycl.* indicates cyclothymia; *Hyp.*, hypomania; *Dem. prae.*, dementia praecox; *Per. dep.*, periodical depression; *Sch.*, schizoid.

abnormalities (Gowers [8]). The most critical consideration of general hereditary relations of epilepsy is a study by Snell,[30] in which are analyzed the histories of 352 patients from the Munich clinic who had cases of true epilepsy (Table 2). The results from this were compared with the statistical studies of Koller and Diem on general hereditary relations of psychotic and nonpsychotic persons. Snell found that in

30. Snell, Otto: Die Belastungsverhältnisse bei der genuinen Epilepsie, Ztschr. f. d. ges. Neurol. u. Psychiat. **70**:1, 1921.

genuine epilepsy hereditary tainting was present in 81.26 per cent. This is about equal to that which exists among psychotic persons in general, namely, 77 per cent., and is somewhat higher than exists among non-psychotic persons, namely, 67 per cent. The transmission is direct in 59.09 per cent. and indirect in 16.7 per cent. Abnormalities occur among 5.4 per cent. of the siblings of epileptic parents.

There is a marked difference in the quality of the taint between the epileptic and the psychotic patient; 18.2 per cent. of the antecedents of psychotic patients have psychoses, while among those of epileptic patients, psychoses are present in only 5.05 per cent. What seems to be of special importance in epilepsy is the marked prominence of nervous diseases among the antecedents of persons with epilepsy. These occur in 28.28 per cent., while among psychotic persons this frequency is only 5.1 per cent. Alcoholism occurs among antecedents of epileptic patients in a percentage of 25.89, which is higher than in any other known group. While statistical researches concerning the presence of alcoholism among parents of epileptic patients show that this is to be found relatively frequently, it has on the other hand been observed that the children of alcoholic parents in general are rarely epileptic. Rüdin [6] in a discussion of this question suggests that "if there exists any causal interrelation between alcoholism of the father and epilepsy of the child, it is probable in the sense that the alcoholic intoxication of the father activates an epileptic family anlage." These results of Snell's study show that hereditary tainting in genuine epilepsy is of far greater significance than for psychoses in general and that direct tainting is especially strong in respect to nervous diseases and alcoholism.

Mendelian Relations.—There seems to be a general agreement that the anlage to epilepsy is transmitted in a recessive way. This is shown in the results from the investigations of Davenport and Weeks,[22] in which are considered the effects of special types of mating. These indicate that epilepsy and feeblemindedness behave similarly in their hereditary relations. They found that when both parents were epileptic or feebleminded, all of the descendants were epileptic or feebleminded. The mating of two parents who have such disorders as migraine, paralyses, chorea or extreme nervousness results in 30 per cent. of descendants who are epileptic or feebleminded. This is not far from the theoretical expectation from a recessive transmission from simplex persons. There are usually abnormalities among the near relations of normal parents who have epileptic offspring.

Hoffman, in a study of a small amount of material from the Munich Clinic came to a similar conclusion—that inheritance in epilepsy is recessive. Contrary to Davenport, he rarely found epilepsy among children of epileptic parents. He recognizes that in this respect there are excep-

tional families, and cites the case of Oberholzer,[31] in which epilepsy was directly transmitted from parent to child through three generations. He suggests that in epilepsy there is a dihybrid factor, and ventures the hypothesis that in the heredity of epilepsy there may be two factors, one of which determines a motor irritability, and the other may be a disorder of an internal secretion. That epilepsy does occur with endocrine disturbances is well known from clinical experience. This is well shown in a study of our own,[32] in which several members of a family had epilepsy and evidence of hypothyroidism, while others showed dystrophy and myxedema and some, feeblemindedness. It would seem to have been shown with certainty that in epilepsy hereditary relations are of importance.

HEREDITY IN FEEBLEMINDEDNESS

It has long been appreciated that hereditary influences have an important relation in the determination of feeblemindedness. Hereditary

TABLE 3.—*Abnormalities in Mentally Defective Persons with a Family History of Neuropsychiatric Disorders*

Abnormalities	Number	Per Cent.
Nervous disease	3,456	36.3
Mental disease	2,855	29.9
Inebriety	3,028	31.8
Mental deficiency	1,752	18.4

considerations in feeblemindedness are made difficult from a lack of any definite knowledge of just what is transmitted to prevent normal mental development and by the varied pathologic conditions that produce feeblemindedness. In statistical surveys, distinctions have not always been maintained between feeblemindedness due to gross brain pathology and feeblemindedness that occurs without gross brain defects. There exists, however, a large group of feebleminded in which hereditary factors seem to be fundamental.

The relative frequency with which abnormalities occur among the antecedents and families of the feebleminded is shown in the compiled statistics on feeblemindedness among the recruits in the late war by Pierce Bailey.[33] Table 3 shows the distribution of these abnormalities among 9,533 mentally defective persons in whose families there was a history of neuropsychiatric disorders.

31. Oberholzer: Erbang und Regeneration in einer epileptische Familie, Ztschr. f. d. ges. Neurol. u. Psychiat. **16**:105, 1913.

32. Barrett, A. M.: Hereditary Occurrence of Hypothyroidism with Dystrophies of the Nails and Hair, Arch. Neurol. & Psychiat. **2**:628 (Dec.) 1919.

33. Bailey, Pierce, and Haber, Roy: Mental Deficiency: Its Frequency and Characteristics in the United States as Determined by the Examination of Recruits, Ment. Hyg. **4**:564, 1920.

If the methods by which these data were secured permit of comparisons with the results of Diem-Koller's investigations, it shows that psychoses are twice as frequent among the antecedents and families of mentally defective persons as among nonpsychotic patients (15.1 per cent.). They are less frequent than among the general average of psychotic persons (45.9 per cent.). They are less frequent than in manic-depressive psychoses (45.8 per cent.), and more frequent than in epilepsy and general paralysis. The most frequent family abnormality is nervous disease (36.3 per cent.). This is far higher than in psychotic persons (14.9 per cent.). The only disorder in which the tainting factor of nervous diseases approaches it in frequency is epilepsy (28.28 per cent.). It far outranks all other psychoses in the frequency with which alcoholism occurs among antecedents (31.9 per cent.). Here again it approximates epilepsy (25.8 per cent.). It is of interest to note that mental defect was present among antecedents and family members in a percentage of 18.5. This contrasts strongly with what has been commonly believed from the results of other investigators who emphasize the high frequency with which feeblemindedness occurs among the families of the feebleminded. It must be borne in mind that the group reported by Bailey only included males, did not include institutional subjects, and did not include all the intelligence levels usually considered in statistical surveys of the feebleminded. They show, however, that heredity is an important factor in the occurrence of feeblemindedness, and that the two factors which are of greatest frequency among antecedents are nervous diseases and alcoholism. In this respect, feeblemindedness differs essentially from the major psychoses and has a certain resemblance to epilepsy. This fact and the well-known frequent occurrence of epilepsy and feeblemindedness in the same family suggest some sort of correlation in their underlying causative factors.

The most detailed information at present available to us regarding hereditary relations in feeblemindedness is to be found in the contribution of Goddard.[34] The methods followed in his compilations are such that they are not easily compared with the fundamental data we have in the studies of Diem and Koller and the special investigations conducted along similar lines. Goddard studied 300 families of feebleminded subjects, and shows convincingly that feeblemindedness occurs with relatively great frequency among other members of the same families. The other factors that are usually considered with regard to the psychoses, as tainting qualities, did not occur in a frequency that indicated any direct or indirect relations of great importance.

34. Goddard, Henry H.: Feeblemindedness, Its Causes and Consequences, New York, The Macmillan Company, 1914.

Among the families of 300 feebleminded persons, there were 164 others who were feebleminded "in such numbers as to leave no doubt as to the hereditary character of the defect."

Mendelian Relations.—Table 4, prepared by Goddard, shows the results realized in different crossing of feebleminded parents. The close correspondence between theoretical mendelian expectations and results realized seems to show that the hereditary relationship of feeblemindedness among the families of the feebleminded follows the rules of a mendelian recessive.

HEREDITY IN EXOGENOUS PSYCHOSES

That constitutional qualities enter into the shaping of psychoses associated with definite pathologic processes in the brain is well known. Clinical experience shows marked differences in the symptoms of organic

TABLE 4.—*Mentality in Children of Feebleminded Parents*

Type of Mating	No. of Matings	Total Offspring	D. Inf. and Misc.	Undetermined Mentality	Feebleminded Offspring		Normal Offspring	
					Actual Findings	Theoretical Expectation	Actual Findings	Theoretical Expectation
FF FF.....	144	749	149	118	476	482	6	0
FF NF.....	122	689	161	166	193	185.5	178	185.5
FF NN.....	18	66	13	19	0	0	34	34
NF NF.....	33	212	39	27	39	36.5	107	109.5
NF NN.....	7	27	2	2	0	0	23	23
Totals.....	324	1,752	364	332	708	704	348	352

F.F. indictes feebleminded parent; N.F., parent normal but with latent abnormality; N.N., normal parent; D.Inf., death in infancy.

brain diseases showing like pathologic lesions, that seem to be best explained by differences in temperaments and individual reaction types. Illustrations of this are the differences in the mental symptoms among patients with general paralysis, senile dementia, alcoholic disorders and the symptomatic psychoses. The same differences that exist in nonpsychotic and psychotic persons in respect to differences in biologic types are present in the organic psychoses. Endogenous qualities intermingle with the effects of disturbances directly caused by structural disease.

There are some organic nervous diseases associated with psychoses, such as Huntington's chorea, and some forms of idiocy, that are preeminently hereditary. There are others, such as the senile dementia, in which general hereditary relations have no more significance than among nonpsychotic patients. In others, notably general paralysis and arteriosclerotic brain disease, there seem to be a few correlations between inherited factors and disease.

HEREDITY IN GENERAL PARALYSIS

It is variously stated in the literature that hereditary factors are present in from 5 to 78 per cent. of cases of general paralysis.

In an investigation carried out according to the method followed later by Sünner in manic-depressive psychoses and Snell in epilepsy, Kalb [35] studied inheritance in the families of 205 persons with general paralysis selected from the Munich Clinic (Table 2). He found that there were 141, or 67.7 per cent., of this series who had an hereditary taint. The abnormalities were in direct antecedents in about 28 per cent. Psychoses of some sort occurred among the antecedents in 26.7 per cent., compared with 15.1 per cent. among nonpsychotic patients. Suicide occurred among the antecedents or family in a percentage of 4.9, which is about equal to that found in families with manic-depressive psychoses, and is three times as great as that which occurs in nonpsychotic patients. In general, one can conclude that in general paralysis the total hereditary tainting about equals that among nonpsychotic patients. The tainting with psychoses is much greater.

There is some evidence that the quality of the tainting factor in the families of paralytic patients has an influence in determining the type of course that the disease will run. When dementia praecox occurred among the antecedents of patients with general paralysis, the disease tended to follow a dementia course. When the clinical symptoms were those of marked affective reactions, manic-depressive psychoses were commonly found among the antecedents.

HEREDITY IN SENILE DEMENTIA AND CEREBRAL ARTERIOSCLEROSIS

There are few facts available that permit any important conclusion as to the part played by inheritance in these disorders. Rüdin,[6] in a recent discussion, has stated that arteriosclerosis and senile dementia have no rôle in the psychoses as hereditary factors. Clinical experience seems to show that there exists a family predisposition to arteriosclerosis, but whether there is a hereditary tendency to arteriosclerotic psychoses has not been investigated. There is some suggestion of an interrelation of arteriosclerosis with the occurrence of the manic-depressive psychoses. One not infrequently finds relatives of patients with manic-depressive psychosis showing effects of arteriosclerosis. It is possible that there is some biologic correlation between the pyknic constitution type as described by Kretschmer [2] and a tendency toward arteriosclerosis and also manic-depressive psychosis.

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35. Kalb, F. W.: Beiträge zur Belastungsfrage bei Paralyse, Ztschr. f. d. ges. Neurol. u. Psychiat. **43**:391, 1916.

HEREDITY IN HUNTINGTON'S CHOREA

From our first knowledge of this disorder, its hereditary nature has always been in the foreground. The discussions concerning heredity in this disease have centered largely in its hereditary relations with epilepsy and whether or not its hereditary character was due to a polymorphous or similar mode of transmission. The entire question of the hereditary relations of this disease has recently been considered in a monograph by Entres.[36] This critical consideration of 516 cases of Huntington's chorea leads him to the following conclusions.

1. Epileptic persons undoubtedly occur in families some of whose members have Huntington's chorea, and there are rare instances of the simultaneous occurrence of genuine epilepsy and Huntington's chorea. Both diseases, however, have a separate mode of origin. An hereditary relation between the diseases probably does not exist.

2. The more one investigates the facts shown in families with Huntington's chorea, the less is one convinced that the ideas of a transmutative or polymorphous or hereditary cycle are valid. There is a similar heredity in Huntington's chorea. 'Some observations seem to show that there are certain diseases that are associated with Huntington's chorea, with which it seems to have some as yet unknown affinity.

3. There are no facts that prove that Huntington's chorea is in any way sex linked.

4. Huntington's chorea follows the law of a hereditary dominant. The proof of this is that Huntington's chorea is inherited in the direct line, and that the descendants of patients with Huntington's chorea who remain free from the disease never transmit it to their children.

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36. Entres, Josef L.: Zur Klinik und Vererbung der Huntingtonschen Chorea, Monog. aus d. Gesamtgeb. d. Neurol. u. Psychiat., No. 27, Berlin, Springer, 1921.

THE CELLULAR BASIS OF INHERITANCE*

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Since I have been asked to review a large field of biologic research in a few minutes, it will be necessary for me to limit the presentation to an elementary outline. At the outset I believe I can do no better than to quote a few sentences from the address of Prof. E. B. Wilson before the Royal Society in 1914 on a similar subject: "The Bearing of Cytological Research on Heredity."

> The aim of cytology, in so far as it bears directly upon the problems of heredity, is to trace out in the individual life the history of maternal and paternal elements originally brought together in the fertilization of the egg. . . . This (aim) has been most clearly realized through the study of the cell nucleus, and in particular of the bodies known as chromosomes. I ask attention especially to these bodies . . . not because the chromosomes are the only elements concerned in heredity, but because they offer the most available point of attack and have in fact yielded the most definite results. The limitations of time compel me to take a good deal for granted, and to pass over, for the most part, the historical and controversial aspects of the subject. I must be content, in the main, to state briefly what I believe to be established or indicated by the evidence.

This statement serves admirably for the present discussion. The nine years which have elapsed since it was made have served to focus attention more closely on the chromosomes as the vehicles of hereditary transmission; and I believe that in the few minutes at my disposal I can accomplish most by confining my discussion to them.

Let us begin, then, with the fertilization of the egg and follow the history of the chromosomes throughout a typical life cycle. The gross features are represented in the diagrams of Figure 1. In constructing these diagrams, I have not taken a hypothetical case, but I have used one with which I am personally familiar—a species of fruit-fly of the genus *Drosophila*.

In this fly, the egg and the sperm each contains three chromosomes, and each of these differs from the other two. When the egg is fertilized, the two groups of chromosomes are brought together, and early in the development of the embryo the chromosomes become associated in pairs. These pairs are composed of homologous elements—one from the father

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* Read before the Association for Research in Nervous and Mental Diseases, December, 1923.

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and one from the mother. During the development of the animal, as the somatic cell divisions progress, each of these chromosomes divides longitudinally at each division, and all cells have the full set of chromosomes associated in pairs. Figure 2 shows how the chromosomes are associated in pairs, and that the pairs are symmetrical, i. e., composed of homologues, with the exception of the small chromosome, which we will consider later.

Ordinary mitotic divisions occur throughout the development of the fly until the germ cells are formed. Then a different process ensues. We have already seen that the somatic cell has twice the number of chromosomes found in the germ cell. If the germ cells had the somatic

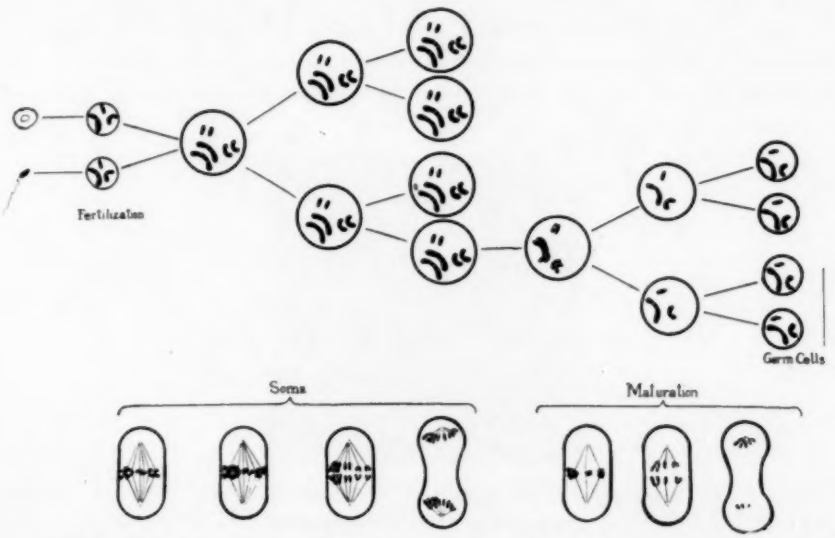

Fig. 1.—Diagram representing the history of the chromosomes during a typical life cycle (fertilization of the egg, development of the embryo, formation of germ cells) in a fly.

or double number, the number would be doubled by fertilization in every generation. But this does not take place, because during the formation of the germ cells a process occurs which reduces the chromosome number by half.

This is the so-called "maturation" process, in which the chromosomes conjugate in pairs and then separate in such a way that one member of each pair goes to one germ cell and the other member to another,, as shown in the diagrams in Figure 1. The egg cell gets one chromosome of each kind and the sperm cell gets one of each kind. Fertilization brings them together again in the double or diploid group. Thus the process is repeated generation after generation.

This is the skeleton outline of the behavior of chromosomes, which represents the usual conditions found in animals and plants, and which applies to both sexes. The only feature which is not of general application is the paired association of the chromosomes in somatic cells. This characteristic is especially prominent in the flies. In most organisms, the chromosomes are present in pairs but do not associate in pairs until the time of germ cell formation. But this point is not significant in the present connection.

GROUP OF CHROMOSOMES FOR EACH SPECIES

Each species of animal and plant has a certain definite chromosome group, which is constant for that species. In many cases, this group appears to be identical in the male and female of the species; but in other cases, an interesting and significant sexual difference is observed. For instance, in some species the female has one chromosome more than the

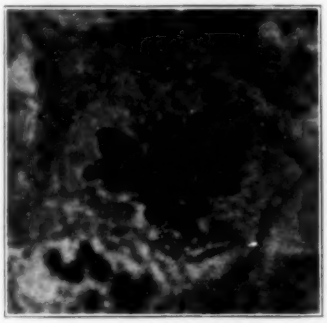

Fig. 2.—Photograph of a spermatogonial chromosome group in a fly (Dasyllis sp.) showing the autosomes associated in pairs and the small (sex) *X* chromosome without a mate.

male. In the female, all of the chromosomes are in pairs. In the male, they are likewise in pairs, except that one pair found in the female is represented in the male by only a single member. This is the sex chromosome or *X* chromosome (the small chromosome in Figure 2). Thus the male has one *X* chromosome and the female two. As a result of this condition, it has been found, as would be expected, that the eggs are all of one kind, each having an *X*, but there are two types of sperm, one possessing and the other lacking the *X*.

When an egg is fertilized by an *X*-bearing sperm, the resulting zygote contains two *X*'s and becomes a female. When fertilized by a sperm without *X*, on the other hand, it contains only one *X* and becomes a male. Since the two types of sperm are produced in equal numbers, the two sexes are represented in approximately equal numbers.

The same principle, slightly modified, applies in other cases. Here the female has two *X* chromosomes as before, but the male, instead of having an unpaired *X*, has an *X* which has a smaller mate called *Y* (Fig. 3). Here also two types of sperm are produced, the *X*-containing and the *Y*-containing. The former is female determining and the latter male determining.

All degrees of size difference are found between that in which the *Y* chromosome is extremely small and that in which it is almost indistinguishable from the *X*. This leads to the conclusion that even in cases in which no distinction is visible between *X* and *Y*, they are, nevertheless, qualitatively different, and the same principles of sex determination hold true. This conclusion is supported by cytologic observations on various

Fig. 3.—Drawings of Drosophila chromosome groups to show paired association of homologous chromosomes and also sex chromosome relations. (1) Drosophila repleta, female; (2) same, male; (3) Drosophila affinis, male; (4) Drosophila obscura, female; (5 and 6) same, males. Note the equality of the sex chromosomes (*XX*) in the females, and the inequality of *X* and *Y* in the males.

forms, and in one case it has been demonstrated (by a combination of genetic and cytologic studies) that *X* and *Y* are qualitatively different even though they look alike—but the data are too detailed to be considered here.

In certain groups of animals the situation is similar, but just reversed, in a sense. Here instead of the female having two *X*'s and the male one, the male has two and the female one, so that there are two kinds of eggs instead of two kinds of sperm. The mechanism, however, works in the same way.

These observations on sex chromosomes have extended over such a wide range of animals, including both vertebrates and invertebrates,

that it is now accepted as an established fact, I believe, that the sex chromosome is the primary agent in sex determination in most animals.

DISTRIBUTION OF CHROMOSOMES

This being the case, let us note again, just how the X chromosomes are distributed. In the typical case, the X-containing sperm is female determining. Consequently the daughters get two X's, one from each parent. On the other hand, the male determining sperm has no X, and as a result the male progeny get only one X and this is from the mother.

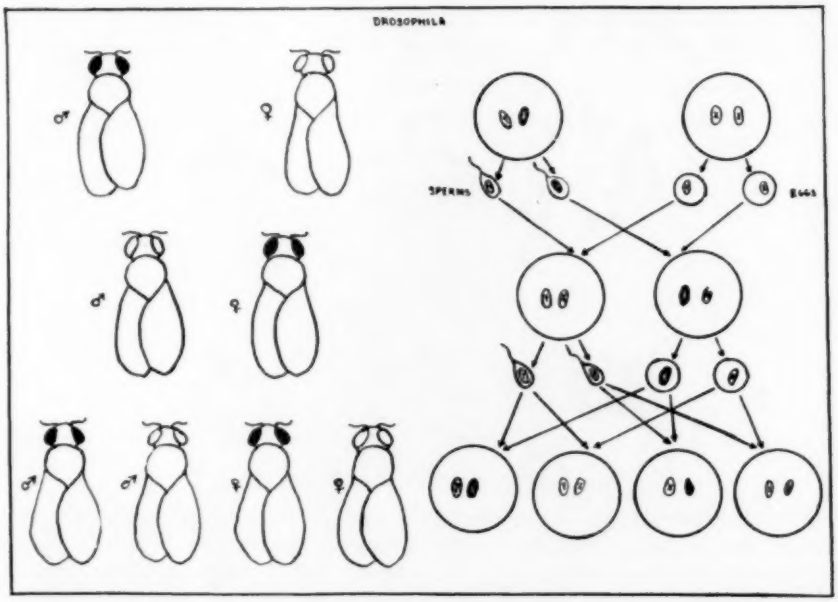

Fig. 4.—Diagrams illustrating the inheritance of the sex-linked character, white eyes, in Drosophila. (From Sharp, after Morgan. Sharp, Lester W.: An Introduction to Cytology, New York, McGraw Hill, 1921.)

FACTS OF INHERITANCE

With this in mind, we may now examine some of the facts of inheritance. I will take an example with which I am familiar. This is the mutant character, white eyes, in *Drosophila melanogaster*. (In the the normal fly of this species, the color of the eye is red.)

If a red-eyed male *Drosophila* is mated to a white-eyed female (white eye being recessive) the sons are all white-eyed like the mother (Fig. 4). The daughters, however, are all red-eyed like the father. In the next generation, the sons are of both kinds, and so are the daughters. Let us follow the distribution of the sex chromosomes in this case and

see the correspondence. In the upper left hand circle in Figure 4, the *X* chromosome of the male is represented in black and the *Y* in white. In the female (at the right), two *X*'s are represented in white. The son gets his *X* chromosome from the mother; the daughter gets both kinds of *X* chromosomes—one *black* from the father and one *white* from the mother—and as a result, the son is white-eyed, and the daughter red-eyed. In the next generation, both types of males and both types of females are produced. The distribution of the characters here is identical with that of the *X* chromosomes. Indeed, it has been demonstrated in this and other cases that the material basis, whatever it is, that is responsible for the character of eye color in this fly is carried by the *X* chromosome. For this reason, such characters are said to be sex-linked.

In the autosomes, or the chromosomes which are distributed equally to both sexes, we find that the same principle applies; and a great many characters are known whose mode of inheritance is identical with that of the autosomes. Take for instance albinism in guinea-pigs as shown in Figure 5. If an albino is crossed to a black, the animals are all colored, because black is dominant (F_1). When inbred, they give in the second generation three colored to one white (F_2). If we follow a pair of chromosomes, assuming them to carry the factors or genes for these characters, we find that their distribution calls for just this result, as is indicated by the lower diagram in Figure 5.

Since an animal may have hundreds of independent mendelian characters, there cannot be a whole chromosome for each character. In the case of *Drosophila* with three pairs of chromosomes, for instance, there must be a great many factors or genes in each chromosome; and, as a consequence, we see also that the genes in any one chromosome should be associated in some fashion, and ought to behave as a group in inheritance. Again omitting details, it may be stated that this has been found to be the case in all of the species adequately studied. Mendelian characters fall into groups because of their tendency to stay together in inheritance. But it has been found that they do not invariably stay together; occasionally they separate, and this separation can, of course, only be explained by assuming a separation of the factors or genes responsible for them. This process of separation of linked genes is called crossing-over.

From the genetic standpoint, crossing-over is a phenomenon of exceptional interest, and it has received extensive study, especially by Professor Morgan and his co-workers at Columbia University. The subject is too complicated for extensive review here, but I will try to give a few of the simpler facts and indicate what appears to be the most probable explanation of them.

In doing this, let us go back in the history of cytology and consider some of the first observations on chromosome behavior. Very early it was recognized that when a chromosome divides in mitosis, instead of merely breaking in two, as it might if merely a mass division were required, it first draws out into a long delicate thread, and then this

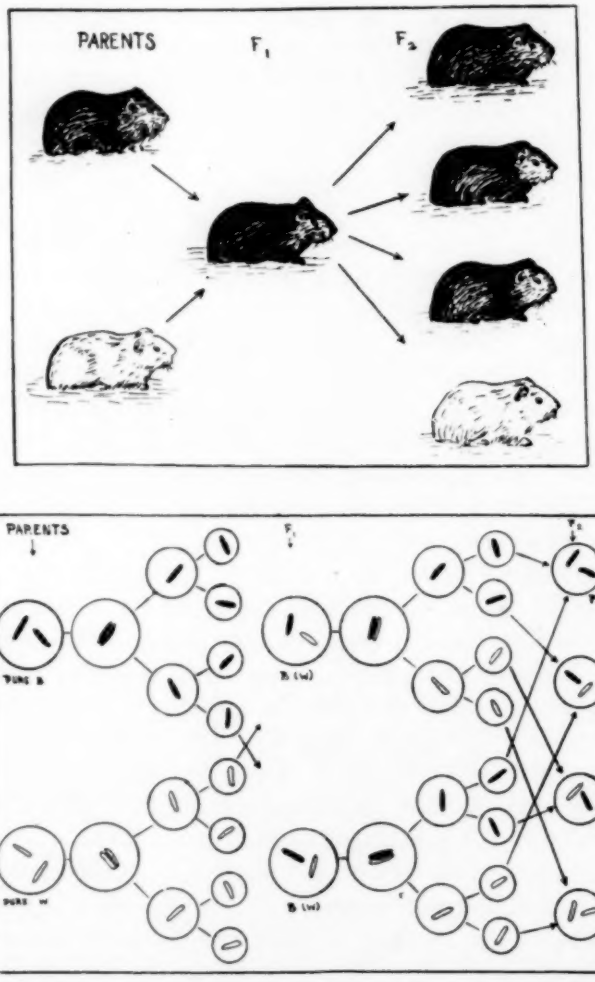

Fig. 5.—Diagrams illustrating the inheritance of the nonsex-linked character, albinism, in guinea-pigs. (After Sharp.)

thread splits lengthwise in a precise manner. This fact led Roux, in 1883, to the conception that the chromosome is not a homogeneous, gelatinous rod, as it might appear to be, but that it is complex in structure and composed of different materials arranged in a linear order throughout the length of the thread. Thus the function of longitudinal

division would be to divide each of these materials accurately and bring about an equal distribution to the daughter cells. This view has received more and more support as cytologic experiments have progressed in recent years, and, as you can see, it fulfils to a nicety the requirements of genetics—which necessitate the assumption of a great number of independent genes being present in the chromosomes.

Figure 6 from Wenrich's study on a grasshopper will serve to indicate that it is actually possible to see something of structure in the chromosome. Each figure in the field represents a pair of chromosomes in an early maturation stage, when the chromosomes are drawn out into threads and the structural differentiation is most evident.

This figure also shows that the two members of the pair have similar chromomeres (lumps or granules) and that any particular pair of chromosomes looks the same in different cells. Each of these figures

Fig. 6.—Chromosomes in a grasshopper, illustrating visible structural differentiation in the chromosome. (After Wenrich. Wenrich, D. H.: The Spermatogenesis of Phrynotettix magnus with Special Reference to Synapsis and the Individuality of the Chromosomes, Bull. Museum Comp. Zool. Harvard **60**: 55-136, 1916.)

represents the same pair of chromosomes, but taken from different cells in the organism. The organization of this particular pair is similar throughout the series. I do not wish to give the impression that these chromomeres actually represent genes. This can hardly be the case. There are a great many more genes than there are chromomeres, and we do not know what connection, if any, there is between them. I am simply giving these facts to show that there is some internal structure to the chromosomes.

If we consider the genes as arranged in a series in the chromosome, we can see that a crossover would occur if an interchange of parts took place between two homologous chromosomes. An opportunity for this is provided by the close union or conjugation of chromosomes during the maturation of the germ cells. It is not known just how the inter-

change of segments is brought about, but it is almost certain that it does occur and presumably at this stage, since this seems to be the only stage which gives a good opportunity for it.

A definite case in which crossing-over is known to occur is that of the mutant characters—yellow body and white eyes—in *Drosophila melanogaster* (Fig. 7). If a yellow-white male is crossed to a gray-red female, the daughters are all heterozygous for these characters. If a daughter is backcrossed to a yellow-white male, the progeny are nearly

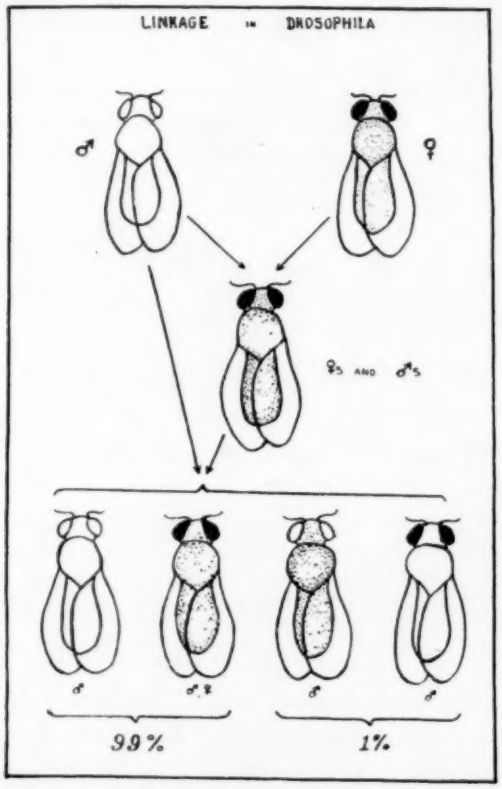

Fig. 7.—Diagrams illustrating linkage between white eyes and yellow body color in Drosophila. (After Sharp.)

all of the two parental types, yellow-white and gray-red, but a few (about 1 per cent.) are of the other two possible types, yellow-red and gray-white. The latter represent the crossovers.

The process may be visualized better, perhaps, by the aid of diagrams (Fig. 8). Suppose the white chromosome at the left carries the genes for yellow body and white eyes, and the black one those for gray body and red eyes. Then an interchange, such as shown, with

the break coming at a point between the two, would result in a cross-over. If three genes were being followed, it would be possible to get a "double crossover" as indicated in the diagram on the right.

It has been found in actual experiments that the amount of crossing-over between different combinations of genes differs greatly. For instance, A and B may give 10 per cent crossing-over, and A and C 20 per cent., etc. It has also been found that if A and B give 10 per cent. and A and C 20 per cent., then B and C will give either the sum or the difference—10 per cent. or 30 per cent. This makes it possible to plot the result in a straight line, with a definite percentage value between successive genes. This fact, in turn, has led to the view that the crossover values depend on the serial order of the genes and their distance apart in the chromosomes. Working on such an hypothesis, it has been possible to test the linkage relations of many genes in one chromosome, and to plot the results in the form of a map, in which the genes appear in a definite sequence and at definite distances from one another, the distances representing crossover values.

Fig. 8.—Diagram representing crossing-over in chromosomes. (From Sharp after Babcock and Clausen.)

The results obtained in this way are not only consistent, but they allow of prediction with a high degree of accuracy. For example, if the crossover percentage of a gene is known with respect to two genes on the map, its crossover percentage with any other known gene may be predicted.

Just how far these maps may be considered as depicting the actual relations in the chromosomes is not yet certain, but it seems probable that they give a fairly true representation in a general way. It is even possible, by means of these maps, to compare individual chromosomes in different species in regard to the genes and their approximate location —and to feel that the comparison is fairly reliable—at least, that it is not altogether visionary.

COMMENT

This has been a hasty review, and therefore somewhat disconnected. I have attempted to make the chromosomes seem realistic and to indicate to some extent the significance of their behavior. They are fascinating objects of study, and to those who work with them they stand

out as individual, self-perpetuating entities, each with its own size, form, behavior and internal organization. If I have neglected other cell structures, it is not because they are nonessential, but because, so far as we know, they do not play such a clear-cut rôle in inheritance as do the chromosomes.

HISTOPATHOLOGIC FINDINGS IN A CASE OF FRIEDREICH'S ATAXIA*

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PHILADELPHIA
AND
JOHN L. ECKEL, M.D.
BUFFALO

Many excellent papers have been published (Blocq and Marinesco,[1] Brissaud,[2] Brissaud and Londe,[3] Déjerine and Thòmas,[4] Dumont,[5] Spiller,[6] Pfeiffer [7] and others) on the pathologic anatomy of Friedreich's ataxia, but its histopathology has not been thoroughly studied.

Friedreich's [8] original article appeared in 1863. Marie,[9] thirty years later, culled from the literature sixteen cases—of which only two contained a necropsy report—which he felt did not belong to the Friedreich group. On the basis of these cases, he established a new clinical syndrome, which he called hereditary cerebellar ataxia. He regarded the symptoms as the result of some congenital defect of the cerebellum.

Since this time, there has been much discussion as to the proper placing of particular cases. Most of the cases have shown mainly cord symptoms and cord pathology. In some, the cerebellum has been more

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* From the Neuropathological Laboratory and Wards of the Philadelphia General Hospital.

* Read at the Fourth Annual Meeting of the Association for Research in Mental and Nervous Diseases, New York, Dec. 27 and 28, 1923.

1. Blocq and Marinesco: Sur l'anatomie pathologique de la maladie de Friedreich, Arch. de neurol., 1890, p. 331.

2. Brissaud: Leçons sur les maladies nerveuses, 1893-1894, p. 43.

3. Brissaud and Londe: Sur un cas d'heredo-ataxie cérébelleuse, Rev. neurol., March 15, 1894, p. 129.

4. Déjerine and Thòmas: L'atrophia olivo-ponto-cérébelleuse, Nouv. iconog. de la Saltpêtrière, 1900, p. 330.

5. Dumont: Contribution à l'étude de l'anatomie pathologique de la maladie Friedreich, Thèse de Lyon, 1902, p. 250.

6. Spiller: Friedreich's Ataxia, J. Nerv. & Ment. Dis. **37**:411, 1910.

7. Pfeiffer: A Case of Hereditary Ataxia (Friedreich's) with Anatomical Findings, Arch. Neurol. & Psychiat. **7**:341 (March) 1922.

8. Friedreich: Ueber degenerative Atrophie der spinalen Hinterstränge, Virchow's Arch. f. path. Anat. **26**:391, 1863.

9. Marie: Sur l'hérédo-ataxie cérébelleuse, Semaine méd., 1893, p. 444.

involved (Fraser [10] and Nonne [11]). In a few, both cord and cerebellum have been involved. It is with the latter group that this paper is chiefly concerned.

REPORT OF A CASE [12]

History.—W. S., a man, single, aged 52, was admitted to the Philadelphia General Hospital, Dec. 17, 1888, at the age of 18, and died, July 3, 1922, in the service of Dr. Charles S. Potts. The patient had walked since the age of 3 years until the age of 15, when he was forced to use a cane because he staggered and was awkward and clumsy in lifting his feet. He managed to walk with the aid of a cane until the age of 25, when he became chair-ridden. At 18, he had attacks of pain in the stomach, associated with nausea and vomiting. He was intelligent, and stated that his speech had always been slow. In childhood, he had measles, chickenpox, scarlet fever and "rheumatism." His father had had some type of paralysis of both legs. One sister had a similar condition and was in the hospital.

In 1898, there was present marked atrophy of the small muscles of both hands with a pronounced atrophy of both legs. His pupils were normal. Lateral nystagmus was present to a slight degree. Vision was good. There was no "Friedreich toe," and a negative Babinski sign on both sides was recorded. The knee and ankle reflexes were absent, and he showed a steppage gait. The Romberg sign was present. Sensation was normal.

In 1905, he had had slight diminution of sensation of both legs and feet, with fibrillary tremor in the atrophied muscles. There was double foot drop. The pupils at this time were found to be unequal, the left being larger; both reacted promptly.

In 1921, he presented the following symptoms: There was some mental weakness. The eyes presented a lateral nystagmus on movement in either direction. The pupils were slightly unequal, the left being a trifle larger. The irides reacted promptly to both light and in convergence; the eyegrounds were normal. The tongue showed a slight tremor. Speech was slow. There was no disturbance of sensation of the face. The hands and forearms showed marked atrophy, with a claw hand. The upper arms were well developed, with the presence of fibrillary tremor in the triceps and also in the atrophied muscles. Except for a slight diminution of vibratory sense, the other forms of sensation were well preserved. The biceps and triceps reflexes were absent. Considerable ataxia was present in the finger-to-nose test on both sides. The lower extremities were cold and cyanotic, and considerable hard edema was present in the feet. The muscles below the knees were greatly wasted, and there was foot drop and flaccidity. The tendon reflexes at the knees and ankles were absent. The muscles of the thighs were small. Fibrillary tremor was present in all the atrophied muscles. Both legs showed marked ataxia. Muscle power at the hips was well preserved. Sensation below the knees was impaired for vibration and position and slightly for tactile sense. Pain and

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10. Fraser: Defect of Cerebellum Occurring in Brother and Sister, Glasgow M. J., 1880, No. 1, p. 199.

11. Nonne: Ein weitere anatomischer Befund bei einem Fall von familiärer Kleinhirnatrophie, Arch. f. Psychiat. **39**:86, 1906.

12. This case was reported clinically by Dr. William G. Spiller in the Journal of Nervous and Mental Diseases in 1910, and we have used the notes with Dr. Spiller's permission.

temperature sensations were well preserved throughout both legs and feet. He was unable to walk. In July, 1922, he became gradually weak and his pulse feeble; râles developed at the bases of the lungs, and he died.

The sister, Ella G., aged 53, was married and had one daughter, who was well and had four healthy children, aged 11, 5, 3 and 2. She was admitted to the Philadelphia General Hospital, April 4, 1899, at the age of 29. She was still in the hospital in the service of Dr. William G. Spiller. Her symptoms began at the age of 14, with ataxia of the upper extremities, then in the lower extremities, and the condition progressed until she became chair-ridden at the age of 33. Her pupils were equal and the irides reacted promptly. Lateral nystagmus was present. Vision was normal. There was slight dysarthria. Intelligence was intact. The upper extremities were ataxic, with atrophy of the hands and forearms and a tendency to a claw hand. The biceps and triceps reflexes were present. Sensation of the upper extremities was normal. The lower extremities showed drop feet, with atrophy of the muscles of the feet and legs with edema. The knee and ankle reflexes were absent. All sensation was slightly lessened below the knees, except sensations of pain and temperature. There was no deformity of the toes. Plantar stimulation gave flexion. Slight scoliosis of the thoracic spine was present.

Necropsy Findings.—In the gross, the brain was of the usual size. The pia-arachnoid was thickened and milky; the convolutions were narrow and the fissures wide, especially over the anterior half of the brain. The vessels were intensely sclerotic. The cerebellum was very small, being about one-half normal size. The pons and medulla were normal. The spinal cord was small. On transverse section of the brain, the ventricles appeared dilated. No areas of softening were found.

For microscopic study, sections were taken from the fresh brain from representative areas of the cortex, pons, medulla and cord and fixed in alcohol. The rest of the brain was put in liquor formaldehydi, and after fixation sections were again taken and the following stains used: hematoxylin-eosin, phosphotungstic acid-hematoxylin, Weigert's myelin sheath stain, Bielschowsky, Alzheimer-Mann, Marchi, Herxheimer, Mallory-Jacob and the combination stains as described by Hassin.

Microscopic Findings.—The pia-arachnoid showed a definite fibrosis but no cell infiltration. The vessels of the cortex exhibited an advanced arteriosclerosis. The cortical layers were somewhat altered because of loss of ganglion cells with a slight increase of glia. The ganglion cells themselves showed various types of chronic degeneration. Betz cells were greatly reduced in number; those that remained showed degeneration, atrophy being the most common finding. Few examples of axonal chromatolysis or satellitosis could be found.

The folia of the cerebellum were small with narrowing of the constituent layers. The molecular layer contained more glia cells than are usually found; basket cells and fibers were lessened; Purkinje cells were very much decreased in number although a few were normal in structure (Fig. 1). For the most part, they were atrophied; some were but shadows of cells with the barest suggestion of a nucleus and vacuolated protoplasm. Lipoid excess could be found in some, but was uncommon. Some cells were found in abnormal locations. The Bielschowsky stain showed either a complete absence of the intracellular structure or a clumping together of the fibrils. The granule layer contained only a fraction of the usual number of cells. The white fibers were diminished. The dentate nuclei showed definite alterations.

The constituent cells were of normal number, but they were in various stages of degeneration; an increase of lipoid and cell atrophy was common. Glial nuclei were increased, and many irregular forms were present. New vessel formation was a prominent feature. The vessels in the immediate vicinity showed a "collaring" with cells which with sharlach R were seen to be "gitter" cells.

The pons and medulla were of normal size, although the restiform body and superior cerebellar peduncles were possibly a little small. The inferior olives showed changes that were identical with those of the dentate nuclei. The ascending cerebellar tracts were thin. The pyramidal tracts showed a diffuse degeneration. The gracile and cuneate nuclei showed changes of a mild degree.

The spinal cord was small. The central canal was open. The posterior columns were degenerated, practically completely below, with much less change

Fig. 1.—Cerebellum, showing sparsity of Purkinje cells and slight heterotopia. Note lessened number of granule cells.

in the tract of Burdach (Figs. 2 and 3). The changes in the posterior roots corresponded to this, being much greater in the lower levels. The pyramidal tracts were thinned out, more markedly on one side than on the other. The direct pyramidal tract was involved at the upper levels. Both cerebellar tracts were moderately degenerated. The anterior horns were narrowed, the roots lessened. The toluidin blue sections showed that the anterior horn cells were lessened in number throughout. The cells that remained showed chronic degenerative changes. Atrophy leading to eventual disappearance of the cell was the predominant feature. Clarke's column contained less cells than normally, and they too were degenerated, but much less than the anterior horn cells. Glial nuclei were increased throughout the cord.

The longitudinal sections of the various levels of the cord gave the most valuable information, especially by the combination of the Bielschowsky and Alzheimer-Mann methods. In the posterior portion of the columns of Goll, where the degeneration was most intense, there was a glial scar containing

large cytoplasmic glia cells and glia fibers with a few naked fine and coarse axis cylinders, in good condition. An occasional fiber with a swollen myelin sheath filled with Elzholz bodies could be made out. In places, the axis cylinders showed bulbous expansions and at times fragmentation. In the areas adjoining, where the damage was less, the swollen myelin sheaths could easily be made out. Here there were a few normal nerve fibers. Others appeared as naked axons; some were broken up into fragments. Other axons were tortuous and showed bulbous thickenings. The myelin sheaths were usually swollen and fenestrated. In places, the course of the fiber was indicated by globules in longitudinal rows containing some degenerated

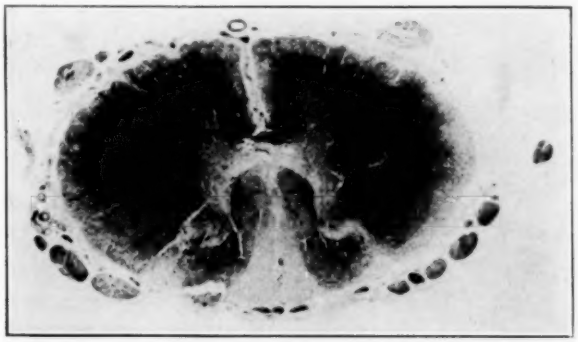

Fig. 2.—Cervical cord. Weigert myelin sheath stain.

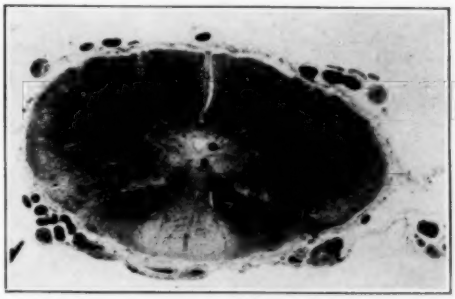

Fig. 3.—Thoracic cord. Weigert stain.

remnants (Fig. 4). These so-called Marchi globules were present even in areas that appeared healthy with the ordinary staining methods. Elzholz bodies were greatly increased. This combination of changes has been found to be characteristic of secondary degeneration (Knick,[13] Jacob,[14] Hassin,[15]).

13. Knick: Ueber die Histologie der sekundären Degeneration im Rückenmark, J. f. Psychol. u. Neurol. **12**:20, 1909.

14. Jacob: Ueber die feinere Histologie der sekundären Faserdegeneration in der weissen Substanz des Rückenmarks Alzheimer, Histolog. und Histopath. Arbeiten **5**:1, 1912; Experiment. Unters. über die Traumatischen Schädigungen des Zentralnervensystems, ibid., p. 182.

15. Hassin: Histopathological Changes in a Case of Amyotrophic Lateral Sclerosis, Med. Rec., February 10, 1917.

The same kind of alteration was present not only in the posterior columns, but in the lateral tracts as well and more strikingly in the pyramidal system than in the cerebellar. Few "gitter" cells were made out within the cord; they were present in the subarachnoid space. The posterior roots showed degeneration, more marked in the lower levels of the cord.

REVIEW OF THE LITERATURE

Our review of cases reported in the literature has been restricted to those cases showing, after postmortem examination, the combined type of the disease, such as we have found in our case.

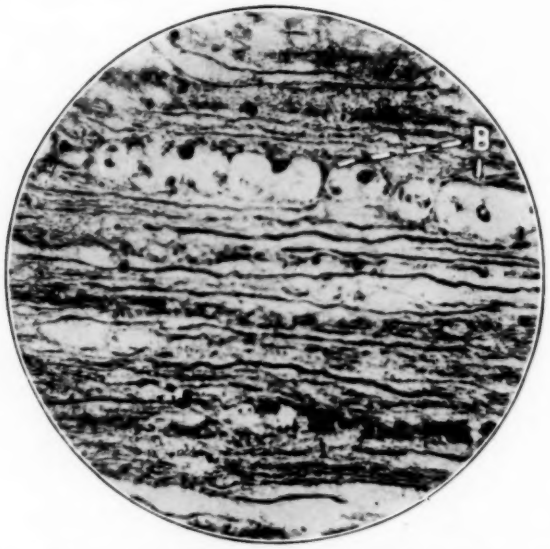

Fig. 4.—Longitudinal section of cord showing Marchi globules at *B*. Bielschowsky stain.

Menzel[16] was the first to report the findings in a case showing changes in both the cord and cerebellum. This case led to considerable controversy, and finally Marie classed it as a mixed type. The patient, a man, who died at the age of 46, had a marked hereditary history. The symptoms began at 17, with difficulty in writing. Ataxic gait developed at the age of 28. At 36, he was unable to write, and at 40, he was unable to walk. He showed disturbance of speech, but no nystagmus. During the latter years, there were a few objective sensory symptoms. The pupils were normal, and the knee reflexes were brisk. Postmortem examination showed marked atrophy of the cord, pons, cerebellum and medulla. The molecular layer of the cerebellum was narrow and the Purkinje cells were reduced in number. Atrophy of the olivary bodies and of the seventh and twelfth nuclei was present. The spinal cord showed degeneration in the posterior column, crossed pyramidal tracts and in both cerebellar tracts. The posterior roots were small. The

16. Menzel: Beitrag zur Kenntniss der hereditären Ataxie und Kleinhirnsatrophie, Arch. f. Psychiat. **22**:160, 1892.

anterior horn cells were diminished in number. Atrophy of the anterior roots was found. The lateral nuclei of the medulla were small. The corpora restiformi were small.

Nonne[17] reported the cases of three brothers, all showing about the same symptoms, except that the onset occurred at different ages; 30, 14 and 10, respectively. He did not classify them definitely, but Marie included them among his original sixteen cases. Two of these came to necropsy. The first brother had ataxia at the age of 30 and later showed speech defect. Two years later, he became mentally weak and was confined to an asylum. He had difficulty with vision, but the irides reacted normally. He had slight nystagmus. Later, slight sensory trouble developed. Steppage gait appeared late. The knee reflexes were normal. Necropsy revealed general smallness of the central nervous system, but the cord, medulla, pons and cerebellum were relatively smaller than the cerebrum. Careful examination of the cord failed to show any tract degeneration. The spinal roots were thinner than normal. The optic nerve was partially atrophied. Histologically, the cerebellum was normal.

In the second case, in which the patient died some years later, the symptoms began at the age of 10 with ataxia, which progressed steadily. He presented involvement of speech, of writing and of the eye muscles. His intelligence was impaired. Ataxic nystagmus was present. Both superficial and deep reflexes were normal. He died of pulmonary tuberculosis. At necropsy, a small brain, weighing 1,030 gm., was found; the cerebellum was relatively smaller, weighing 110 gm. The medulla was small. There was a thinning of the third and fourth cranial nerves. The olivary bodies and the nuclei of the cerebellum were normal. The spinal cord was of normal size and showed no degeneration.

Klippel and Durante[18] reported the clinical histories of two brothers and a sister, which Marie included in his original article. Later, all these cases came to postmortem, and careful studies were made of the nervous system. Klippel and Durante themselves reported the findings in the first case. The disease began with ataxia of the extremities, impaired speech, and later eye trouble and some sensory disturbance developed. The patient also had club feet and scoliosis. Eventually, he developed the symptoms of a spastic paraplegia, with Babinski sign. He died of tuberculosis. Necropsy revealed a small central nervous system, especially a small spinal cord. The posterior roots, the gray matter of the anterior horns, Clarke's columns, the sensory nuclei of the medulla, all showed moderate atrophy. Goll's column in the cervical region was somewhat degenerated. Both cerebellar tracts were involved in the cervical region. The corpora restiformi were small. Histologically, the cerebellum was normal.

Thomas and Raux[19] reported the necropsy findings in the second brother. His symptoms had been similar to those of the others, except that he did not show spastic paraplegia. The morbid findings were a small brain, cerebellum, pons and medulla, and an especially small spinal cord. The nerve

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17. Nonne: Ueber eine eigentümliche familiäre Erkrankungsform des Centralnervensystems, Arch. f. Psychiat. **22**:283, 1891. Also footnote 11.

18. Klippel and Durante: Contrib. á l'étude des affectiones nerveuses familieles et héréditaires, Rev. de méd., 1892, p. 467.

19. Thomas and Raux: Sur une forme d'hérédo-ataxie cérébelleuse a propos d'une observation suivie d'autopsie, Rev. de méd., 1901, p. 762.

roots of the cord were thin. Microscopically, there was degeneration of the columns of Goll, most pronounced in the cervical region, of Clarke's columns and of Gowers' tracts, in both dorsal and cervical regions. Thinness of both anterior and posterior roots, especially in the lumbosacral region, was noted. Slight involvement of the ventrolateral column was present. There was moderate atrophy of the lateral nuclei of the medulla, and the corpora restiformi were small. Histologically, the cerebellum was normal.

Vincelet[20] and Switalski[21] reported the findings in the case of the sister. They apparently did not agree on the interpretation, for the former reported the findings as those of Friedreich's type, while the latter thought it belonged to that of Marie. The cord was small, with sclerosis of the posterior columns and of the cerebellar tracts. The nucleus gracilis showed degeneration. The corpora restiformi were small. The remainder of the medulla was normal histologically, but was small. The pons showed a diminution of fibers of the middle cerebellar peduncle and a thickening of the subependymal tissue of the fourth ventricle and about the aqueduct. The fissures of the cerebellum were deep and wide. Minute changes were found between the molecular and granular layers. The optic nerve showed some thinning and diminution of the large fibers.

Meyer[22] and later Barker[23] made reports of necropsy findings in three cases from the series of Sanger Brown.[24] These cases had been included in Marie's first sixteen cases before the report on the pathology was published.

Meyer's patient, at the age of 45, had developed symptoms of ataxia of the lower extremities and later of the hands. Visual disturbances were noted. The knee reflexes were present. Speech was thick. She remained mentally clear. No sensory symptoms could be made out. Postmortem examination revealed a normal-looking cerebellum with small folia. No microscopic lesions of the cerebellum were found. The efferent cerebellar tracts showed some involvement. Goll's tracts in the cervical region showed slight changes. The peripheral sensory elements were somewhat involved. The cells of Clarke's column were diminished. The olivary bodies were normal. The optic nerve was atrophied.

Barker reported the other two cases that came to necropsy. The patients were brothers. Their symptoms had been similar and had begun at the age of 20 and progressed until death. Barker felt that the entire central nervous system was smaller than normal, but that this was relatively more marked in the cord and cerebellum. The white and gray matter of the cord both showed degeneration. This same degeneration was present in the pons and medulla, affecting chiefly the cells and fibers of the centripetal paths, including the

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20. Vincelet: Etude sur l'anatomie pathologique de la maladie de Friedreich, Thèse, Paris, 1900.

21. Switalski: Sur l'anatomie pathologique de l'hérédo-ataxie cérébelleuse, Nouv. iconog. de la Salpêtrière, 1901, No. 5, p. 373.

22. Meyer: The Morbid Anatomy of a Case of Hereditary Ataxia, Brain **20**:276, 1897.

23. Barker: Description of Brain and Spinal Cord in Hereditary Ataxia, The Decennial Publication of the University of Chicago **10**, 1903.

24. Brown: Hereditary Ataxia with a Series of Twenty-One Cases, Brain **58**:250, 1892.

posterior column, the nucleus of Clarke, the direct cerebellar tract and its continuation into the restiform body. The cerebellum showed no histologic change, except possibly a diminution of cells in the nuclei dentati and fastigii. The crossed pyramidal tract was normal. The cerebral cortex was normal.

Miura[25] reported a case showing the ataxia and the general symptoms of Friedreich's disease, but necropsy disclosed a small cerebellum, medulla and cord. The cortex of the cerebellum was narrow. Slight atrophy of the optic nerve was found. Microscopically, the cord, medulla and cerebellum were normal.

Mott's[26] case began with ataxia of the gait at the age of 16. The symptoms progressed, and later mental symptoms developed, and he was placed in an asylum. The fully developed case showed scoliosis, talipes equinus, weakness of the muscles, absent tendon reflexes, normal sensation and normal pupils, with speech defect and marked incoordination. Death occurred at the age of 37 from heart disease. Necropsy disclosed wasting of the upper portion of the cerebral convolutions, atrophy of the Betz cells, narrowing of the cortex in the parietal region, diffuse sclerosis of the internal capsule and of the pyramidal tracts of the crus. The crossed and direct pyramidal tracts in the cord showed sclerosis. The cerebellar tracts were sclerosed. Clarke's column was atrophied. There were atrophy and disappearance of many cells in the spinal ganglia. The posterior roots and their extensions into the cord were thin. The peripheral nerves were somewhat involved. Lissauer's tracts were normal. The muscles showed slight wasting. The anterior horn cells were normal. The dentate nucleus showed degenerative atrophy.

Heubner[27] had under his care for two years the daughter of Menzel's patient, who, at the age of 6, developed ataxia of the fingers. She was the sixth child and the only one affected. The Romberg sign developed later, with ataxia of the lower limbs. She had no nystagmus. The pupils, knee reflexes and sensation were normal, and there were no palsies and no muscle atrophy. The symptoms progressed, and she was placed in a sanitarium, where she died at the age of 15. The report of the necropsy was sent to Heubner. The gross findings were marked atrophy of the cerebellum and a small cord. The cord showed combined system degeneration similar to that of her father, while in the cerebellum there was no histologic change.

Neff[28] reported a series of thirteen cases, one coming to necropsy. The symptoms began rather late and were manifested by a marked ataxia of the extremities, dysarthria and some visual disturbances. The knee reflexes were present and the pupils were normal. She was mentally clear, except for periods of depression. Necropsy revealed a small cerebellum and a degeneration of the cerebellar tracts. The cerebral vessels were markedly sclerosed. The findings in this case resemble somewhat those described by Marie and

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25. Miura: Ueber l'hérédo-ataxie cérébelleuse Marie, Mitth. des med. Facultät der Kaiserlichen Japan Univ. zu Tokio **4**, No. 1, 1898; Neurol. Centralbl., 1899, p. 132.

26. Mott: A Case of Friedreich's Ataxia with Post Mortem, Arch. Neurol. **3**:180, 1907.

27. Heubner: Ueber hereditäre Ataxia, Charité-Ann. **31**:115, 1907.

28. Neff: A Report of Thirteen Cases of Ataxia in Adults with Hereditary History, Am. J. Insan. **51**:365, 1894-1895.

his co-workers in their more recent publications on the pathology of hereditary cerebellar ataxia (Marie and Foix,[29] Marinesco and Trêtiakoff,[30] Foix and Trêtiakoff[31]).

COMMENT AND SUMMARY

A case is described that was studied for thirty-four years in a hospital. The diagnosis was Friedreich's ataxia. The picture and the course were typical, with the additional symptom of atrophy of the distal muscles of the extremities. At necropsy, an abnormally small cerebellum and cord were found. Histologically, the cerebellum showed a degenerative process still progressing, while the spinal cord showed a secondary tract degeneration, especially in the posterolateral regions. The ganglion cells of the cortex, cerebellum and spinal cord were in various stages of degeneration, cell atrophy being the most common finding.

Neither clinically nor pathologically is this case in keeping with the doctrines laid down by Marie and his co-workers that in cases with a small cerebellum the posterior part of the cord is little affected, if at all. American and German neurologists have refused to accept such an arbitrary division, as was so well expressed by Patrick.[32] The prevailing opinion is that all these cases belong in one group.

The histologic study of our case indicates that there has been a gradual and progressive death of one neuron after another. It is not an inflammatory but a degenerative process, with glial replacement, and fits in with Gowers' hypothesis of an abiotrophy. It is worth noting that the vascular sclerosis was out of proportion to the age of the patient, a fact which other observers have also recorded.

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29. Marie and Foix: Lésions médullaires dans quatre cas d'hérédo-ataxie cérébelleuse, Rev. de neurol., 1914, p. 797.

30. Marinesco and Trêtiakoff: Trois cas de maladie de Friedreich, Rev. de neurol., 1920, p. 113.

31. Foix and Trêtiakoff: Les lésions médullaires au cours de l'hérédo-ataxie cérébelleuse de la maladie de Friedreich et de la paraplegie spastique familiale, Bull. et mêm. Soc. méd. d. hôp. de Paris **44**:1140, 1920.

32. Patrick: Hereditary Cerebellar Ataxia with Report of a Case, J. Nerv. & Ment. Dis. **29**:129, 1902.

PATHOLOGIC PROCESSES IN EXTRANEURAL SYSTEMS OF BODY IN VARIOUS HEREDITARY AND FAMILIAL NERVOUS AND MENTAL DISEASES *

IS THERE A FUNDAMENTAL SIMILARITY OF THESE?

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Cases of hereditary and familial nervous diseases are comparatively rare, and complete necropsies of such cases are still more infrequent, although during past years a substantial amount of necropsy material has accumulated in several neurologic centers; the attention of investigators, with few exceptions, has been focused on the nervous system alone, or, as in cases of dystrophies, on the neuromuscular apparatus, and the extraneural systems have been more or less neglected. Of the numerous clinical and pathologic reports in the literature, few give the findings in detail.

Of the two great integrating mechanisms of the body, the nervous, and the circulatory system, the latter until recently has not received the attention its importance in this rôle should justify, since through its action, mechanical, metabolic and endocrine integrations are accomplished, and variations in structure and the alterations in function occurring therein may produce varying degrees of disorder in the organism as a whole.

In order to attack the problem under discussion, some classification or systematic arrangement of the disease groups must be followed. It has lately been emphasized by Schaffer [1] that heredodegenerative conditions of the nervous system show clinical similarities in certain typical features, among which are familial appearance, homochronicity, homotypism, homotopism and a more or less strikingly progressive course. According to Jendrassik,[2] the symptom grouping is the essential one, and his classification with the diseases arranged according to symptomatology is comprehensive, but there are innumerable transition forms which do not permit of sharp categorical arrangement.

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* Read at the Fourth Annual Meeting of the Association for Research in Nervous and Mental Diseases, New York, Dec. 27, 1923.

1. Schaffer, K.: Die allgemeine histopathologische Charakterisierung des Heredodegeneration, Schweiz. Arch. f. Neurol. u. Psychiat. **7**:193, 1920.

2. Jendrassik, E.: Die Hereditären Krankheiten, in Lewandowsky: Handbuch der Neurologie **2**, 1911.

For the purposes of the present study, cases showing degenerative manifestations were classified according to Bing,[3] as follows: (*a*) predominantly motor (as in the spastic and dystrophic), (*b*) predominantly sensory (as in the spinal and cerebellar ataxias), (*c*) dyskinetic (as in myotonia, myoclonia, chorea, etc.), and (*d*) predominantly mental (as in the idiocies, and possibly the inherited tendencies in some of the mental disorders).

There is considerable unity of opinion among investigators that at least some types of mental disorders, epilepsy and feeblemindedness may be inherited, and that there is even such a basis for the background of certain temperamental expressions. Conklin [4] writes that notwithstanding noteworthy exceptions, which may be due to remarkable variations, Galton's statistics [5] show the trend of genius in certain families, the investigations of Goddard,[6] of Davenport [7] and Weeks [8] prove that feeblemindedness and epilepsy are also inherited, and the work of Mott [9] and Rosanoff [10] indicates that some types of mental disorder are also transmitted in the germ plasm.

THE GROUP OF DYSTROPHIES AND MYOPATHIES

While it is not the function of this paper to discuss in detail the pathology of these conditions, a few remarks must be made regarding the important features of each extraneural system of the body from the standpoint of localization of lesions. A few postmortem reports were found in the literature describing in some detail the gross and microscopic lesions; however, generally speaking, neuropathologists seem to have been contented with the examination of the nervous system and of parts of the voluntary muscles; therefore there is still much to be done in determining the degree, if any, of alterations in smooth muscle and the viscera.

The following statements are based on a few cases gleaned from the literature and from histopathologic examinations made on six cases of myopathy by the author.

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3. Bing, R.: Entwicklung und gegenwärtiger Stand der Anschammgen über heredofamiliäre Nervenkrankheiten, Ergebn. d. inn. Med. u. Kinderh. **4.**

4. Conklin, E. G.: Heredity and Environment, Ed. 5, Princeton, N. J., Princeton University Press, 1922.

5. Galton, F.: Hereditary Genius, London, 1892.

6. Goddard, H. H.: The "Kallikak" Family, New York, 1912.

7. Davenport, C. B.: Heredity in Relation to Eugenics, New York, Henry Holt & Co., 1911.

8. Weeks, D. F.: The Inheritance of Epilepsy, Problems in Eugenics, **1.**

9. Mott, F. W.: Heredity and Eugenics in Relation to Insanity, London, 1912.

10. Rosanoff, A. J.: The Inheritance of the Neuropathic Constitution, J. A. M. A. **58:**1266 (April 27) 1912.

A. The Muscular System.—So numerous are the subclasses and transition forms of the myopathies that definite pathologic descriptions are impossible, and, moreover, there have been and are still differences of opinion based on histologic examinations in given cases as to whether the changes in the dystrophic muscles are primary or secondary in occurrence, and there is much overlapping between pseudohypertrophic, atrophic, spastic and contracture phenomena.

The findings in the skeletal muscles of the personal cases of progressive muscular dystrophy may be summarized thus:

The fibers of the vastus externus muscles of the thighs were unusually large (perhaps not hypertrophied) and showed the characteristic increase in the nuclei of the sarcolemma. These nuclei were often fused and lobulated, and in places definitely outlined the muscle fibers. The fibers of the rectus femoris were largely replaced by dense fibrous tissue and fatty structure; fatty connective tissue filled with thickened and obliterated vessels composed the principal picture of the sections, although running in narrow streaks were remnants of former muscle fibers, which were atrophied, sclerosed, and characterized by long strings of sarcolemma nuclei in rosary formations. There were no normal muscle cells encountered and nothing that could be interpreted as the normal nucleus of a muscle cell (Fig. 1).

In general, sections of the gluteus maximus showed less of the dense connective tissue replacement than the other muscles, but the substance was in stages of active degeneration since there were many fibers undergoing pseudohypertrophy. There were diffuse sarcolemma cell proliferations, and the tissue in general was badly damaged.

Sections of flexor muscles of the arms exhibited small muscle fibers but no typical pathologic changes, except some cloudiness of the general structure.

The interosseous and thenar muscles were largely reduced to connective tissue elements, and no individual muscle fibers could be traced in these areas. Blood vessels were everywhere thickened, obliterated and surrounded by wide zones of connective tissue. Calcification and areas of pigment deposit were of universal distribution.

The foregoing account is a mere repetition of what has been commonly found in the advanced cases of dystrophy. The examination of a case of amyotonia congenita reveals the more acute picture.

The fibers of the diaphragm were fairly well preserved, staining a normal pink and showing only an occasional area of swelling and albuminous change. There was little increase of connective tissue between the bundles, but there was considerable proliferation of the sarcolemma nuclei. As a general estimate, there was twice the number of sarcolemma cells ordinarily seen, and whorls of these cells were accumulated in clusters about the blood capillaries.

The sartorius was badly damaged and exhibited many areas of swollen and opaque fibers alternating with those reduced to dense shreds of nuclear formation. In patches, it was hardly recognizable as muscle tissue, but resembled the structure of a fibrosarcoma.

The biceps muscle showed a comparatively greater number of fibers retaining the appearance of functional possibilities, but in sections there was dense nuclear proliferation to the exclusion of all signs of muscle tissue (increase in both sarcolemma and muscle nuclei). In all sections examined, the muscle remnants retained the cross striations (Fig. 2).

In the narrow strips of intercostal muscles, a few muscle fibers remained, but the substance was practically entirely replaced by proliferating supporting cells. Great masses of these cells filled the microscopic field. In some areas, the muscle fibers showed lack of development, retaining fetal characteristics. The blood vessels were universally thickened.

Such expressions of degeneration as pseudohypertrophy, atrophy, splitting and fragmentation, sarcolemma proliferations, vacuolization, fatty alteration, vascular changes and general fibrosis have been described in given cases in the literature as present or absent and general or focal; the various combinations and distribution of lesions with or without neural involvement have led to the formulation of the well-known descriptive syndromes.

The conclusion is that the progressive muscular degenerations as a group are due to a primary defect in the skeletal muscle anlagen, the various syndromes of different authors representing localizing tendencies of early embryonic distribution of the inherited factors frequently combined with primary central nervous system involvement.

B. The Osseous System.—Many types of bony deformities, such as skeletal anomalies, deformities of the spine, thorax, fingers and toes, trophic changes in the skull and other bones, dwarfism, giantism and developmental bony asymmetries, disproportions and distortions associated with progressive muscular dystrophy have been described. Several cases in which there were bony changes similar to acromegaly have been reported (Bregman, Eulenberg, Janney, Goodhart, Isaacson), pointing to pituitary involvement. In a case of progressive muscular dystrophy reported by Boggs,[11] there were pathologic changes in the muscles, nerves, bones and particularly the formation of multiple congenital osteochondromas.

An hereditary dystrophy (chondrodystrophy) may occur primarily in the cartilages, of which excellent examples are given by Falta,[12] and

11. Boggs, quoted by Janney et al.: The Endocrine Origin of Progressive Muscular Dystrophy, Arch. Int. Med. **21**:188 (Feb.) 1918.

12. Falta, Endocrine Diseases, Ed. 3, Philadelphia, P. Blakiston's Son & Company, 1923.

Fig. 1.—Thigh muscle in progressive muscular dystrophy showing atrophy, fibrosis and fatty replacements.

Fig. 2.—Biceps muscle in amyotonia congenita showing a few nearly normal fibers but marked regional proliferation of border and perimysial nuclei.

I have recently had the opportunity to study a type of this dystrophy in an infant through the courtesy of Major James F. Coupal, Curator of the Army Medical Museum, who will report the case in full later.

This child, weighing 9¼ pounds (4.2 kg.), and dying a few minutes after birth, was born of a mother on whom a thyroidectomy had been performed six years previously. The gross picture consisted of shortening of the base of the skull, retraction of the root of the nose, shortening and thickening of the extremities and rotation of the lower limbs. The hands were broad and short, the fingers funnel shaped and showed serial constrictions corresponding to the joints. Roentgenograms of the body showed among other things the typical "S" shaped clavicles, the prominent ribs, the shortened bones of the extremities and the very small scapulae. The bones of the head were well calcified.

The general pathologic findings were: moderate pulmonary congestion and atelectasis, acute myocarditis, retarded development of the liver and pancreas, with hypertrophy of the glandular portion, and underdevelopment of the posterior lobe of the pituitary gland. A particularly interesting feature of this case was the condition of the thyroid, which was atypical, showing none of the true fetal characteristics, but showing a type of cystic degeneration and interstitial fibrosis usually seen in an adult gland. Is there a relation between the probable subthyroidism of the mother, the thyroid exhaustion of the fetus and its chondrodystrophy? Are there two varieties of chondrodystrophy, one hereditary and the other developmental?

C. Connective Tissues and Fat.—These tissues show much variation in amount and distribution in different types of cases, but in practically all of the hereditary nervous diseases these tissues as a whole are increased. When there is an excess of fat it is frequently difficult to differentiate this tissue from the pale "fish flesh" appearance of the degenerated muscle, and in the progressive spinal muscular atrophy of infants the body may be so well covered by fat that gross muscle wasting may not be easily noted.[13]

Through the several extraneural systems of the body there are wide bands of connective tissue and abundant fatty alterations, but true fibrosis is not quite so characteristic, although frequently found.

The foregoing facts may indicate the presence of a slowly destructive influence of some circulating toxin or toxins released by the progressively degenerating muscles or other structures, a toxin destroying cells in general (both parenchymatous and mesoblastic), while in any attempt to reconstruct the tissue the simple cells (connective tissue types) reproduce much more rapidly and thus tend to replace the higher types of parenchymatous structure.

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13. Batten, F. E., and Holmes, G.: Progressive Spinal Muscular Atrophy of Infants, Brain **35**:38, 1912.

D. Skin and Appendages.—Owing to the interest in endocrinology, more attention has been paid to the skin structures in later years than formerly, so that in more recent reports of cases of progressive muscular dystrophy, descriptions are found of dryness, corrugations, abnormal pigmentations and seborrheic disorders of the skin, also abnormal distributions of the hair, with scanty or superabundant growth, and trophic disorders in both hair and nails; all, when associated with certain other phenomena, contribute to a theory of endocrine imbalance which in some instances seems to be primary, in others secondary or contributory to the picture as a whole.

E. Circulatory System.—In only a few instances [14] have the heart muscles been adequately examined; however, recently [15] special attention has been directed to the subject, and evidence has been submitted to prove that the heart muscle does not entirely escape the myopathic process characteristic of progressive muscular dystrophy.

The lesions described have been forms of chronic fibrous myocarditis with degenerative atrophy, hypertrophy of fibers and scar tissue formations. In one of my cases,[16] the heart muscle was relaxed and soft and showed some surface fatty alterations. The right ventricle was very thin and soft, and the left ventricle showed a moderate amount of visible interstitial replacement. All heart valves were thickened and sclerotic, and the aorta was much thickened.

Microscopically the heart muscle fibers were thin, the muscle cells elongated and fairly heavily pigmented. The striations were easily seen and the nuclei of the muscle cells were well stained, and regular in size and contour; a large amount of interstitial myocarditis was present in all sections, but in some places it had largely replaced the normal muscle structure. The visceral pericardium evinced localized accumulations of fibrous tissue.

In another case of progressive muscular dystrophy, personally examined, the heart muscle was in an advanced state of chronic myocarditis with patches of complete replacement by connective tissue (Fig. 3). Many fibers showed extensive degeneration, with fatty alterations and replacements, these areas alternating with those of fiber hypertrophy.

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14. Bunting, C. H.: Chronic Fibrous Myocarditis in Progressive Muscular Dystrophy, Am. J. Med. Sc. **135**:244, 1908. Potter, F. C.: Pseudohypertrophic Muscular Dystrophy—A Pathologic Study, New York M. J. **90**, August 28, 1909. Goodhart, S. P., and Globus, J. H.: On the Nature of Muscular Dystrophies with a Report of Changes in Cardiac Muscle in Two Cases, Neurol. Bull. **1**:387, 1918.

15. Globus, J.: The Pathologic Findings in the Heart Muscle in Progressive Muscular Dystrophy, Arch. Neurol. & Psychiat. **9**:1 (Jan.) 1923.

16. Lewis, N. D. C.: A Case of Progressive Muscular Atrophy with Compensatory Mental Reactions, Med. Rec., Dec. 3, 1921.

The muscle nuclei exhibited many bizarre distortions, atrophies, hypertrophies, and in some areas were not well stained. The blood vessels showed notable degenerative changes.

A third observation on the heart tissue from a case of amyotonia congenita is of interest in this connection. There were no actual degenerations seen, but the muscle fibers were small and infantile in appearance, and there was an increase everywhere of nuclear structures, both in and between the muscle cells (Fig. 4); the cross striations of

Fig. 3.—Heart muscle from a case of progressive muscular dystrophy, showing degenerations, hypertrophy of muscle cells and an advanced degree of connective tissue replacement.

the fibers were well preserved. This change gave the appearance of an early myocarditis and perhaps might be termed an irritative myocarditis. Here the early tendencies to interstitial cell proliferations are well emphasized and would indicate that the heart muscle lesions are a part of the disease, and may play an important part in its termination; however, the evidence submitted is not sufficiently convincing as to whether

such lesions are part of the general muscular degeneration or are merely the result of excess strain on the heart or to metabolic disorders of another nature.

Hypoplasia of the aorta, general arteriosclerosis and vasomotor disturbances have been observed in cases of progressive myopathy.

F. Respiratory System.—With the exception of acute bronchopneumonia, to which the majority of these patients succumb, healed tuberculosis is one of the most frequent necropsy findings; however, in my

Fig. 4.—Heart muscle from a case of amyotonia congenita showing small, infantile muscle fibers, exhibiting an irritative phenomenon with an increase in interstitial nuclei.

personal group, the lesions of chronic interstitial pneumonia with thickening of the blood vessels, bronchi and alveolar walls, compensatory dilatations of alveoli, presence of pigment laden cells, swollen vacuolated endothelial cells and small intrabronchial budding proliferations of epithelial cells were regarded as characteristic. In addition, the acute vascular, bronchial and cellular reactions of terminal bronchopneumonia were present.

These respiratory tissue reactions are undoubtedly due to long continued irritation of the structures, perhaps both from endogenous toxins and from inadequate functional activity because of the diseased state and alteration in function of all of the accessory muscles of respiration.

G. Gastro-Intestinal System.—The stomach and intestines with their associated digestive glands have usually escaped careful scrutiny, although some descriptions of cases of muscular dystrophy have included cloudy swelling and chronic passive congestion of the viscera, small, irregular and fatty livers, small stomachs, enlarged and supernumerary spleens and macroglossia.

In cases personally examined, the pancreas showed only a moderate connective tissue increase, and in most sections the acini were apparently functioning well, but there were small areas of fatty necrosis and autolysis. The islands appeared large but distorted and spread out over a large surface; however, some were average in size, and there was no sclerosis. The blood vessels were moderately thickened.

The liver exhibited throughout a great shrinkage and an advanced fatty alteration in the hepatic cells; and the widened intercellular spaces contained a thin granular exudate, probably composed of the substance of the disintegrating cells. Both portal and hepatic vessels were thickened, and there was a general increase in connective tissue, which was pigmented and heavily infiltrated with lymphocytes.

The smooth muscle tissue of the gastro-intestinal tract has usually been described as free from involvement, although Bunting [17] has described a case in which the muscle fibers of the stomach shared in the general muscular degeneration. Additional observations must be made to settle this important point and many questions concerning the accessory digestive glands.

H. Genito-Urinary System.—Reports of cases have rarely failed to mention some form of chronic nephritis which is not infrequently complicated by pyelitis or by multiple miliary abscesses. The kidney substance is usually sclerotic, its surface pitted and granular and the capsule adherent. Microscopically, the kidney tissue reveals a severe degeneration in all parenchymatous structures. Many glomeruli undergo complete hyaline degeneration and fibrosis. Also in the foreground are interstitial changes throughout the organ, with thickening and hyaline alterations of the capsules of Bowman and of the blood vessel walls. Intertubular fibrosis and dense lymphoid infiltration complete the productive picture.

Chronic cystitis and hypertrophy of the prostate have been mentioned in the literature, but more important evidence is occasionally noted in a

17. Bunting: Footnote 14.

hypoplasia or hyperplasia or atrophy of the external genitalia (penis and testicles) associated with other features of endocrine disorders [18]

I. The Endocrine Glands.—The endocrine system has received special attention. The thyroid, suprarenal, pituitary, thymus, pineal, gonadal and combinations of these theories, have been proposed to account for the clinical manifestations in numerous case reports.[19] Certainly there is sufficient evidence to justify the conclusion that the endocrine glands are involved in the muscular dystrophies, and recent studies in metabolism have indicated a similarity in the metabolic pictures of progressive muscular dystrophy and the maladies of unquestionable endocrine origin, such as myxedema, hypopituitarism and Addison's disease.

In some instances, the thyroid gland seems to bear a relation to muscular dystrophy. Boveri [20] has reported several muscular dystrophy cases in which exophthalmic goiter was also present; von Werdt [21] reported a case associated with colloid struma of the thyroid and changes in the other glands, and Hellmut-Maiweg [22] laid special stress on thyroid hypoplasia in the pseudohypertrophic form of muscular dystrophy and also on the general disturbances of function of the thyroid and parathyroids.

In some of my cases, the thyroid gland was small, firm and pale, with large traversing bands of connective tissue and a reduction of colloid substance. Microscopic examinations revealed a dense fibrous tissue stroma, in which there were many disorderly accumulations of epithelial cells. The acini were small and frequently occluded by thyroid epithelial cells with deeply stained abnormal nuclei.

In one instance, the thyroid presented an unusual appearance in that the gland was well divided by wide fibrohyaline bands of tissue, containing thickened vessels and enclosing groups of thyroid epithelial cells arranged in small, infantile, acini, containing no colloid. The epithelial cells were very small, but retained the usual staining properties in the nuclei. There were many small hemorrhages through the gland, but the general picture was that of regression (Fig. 5).

The thyroid from a case of amyotonia congenita exhibited alveoli which were greatly reduced in size and numbers, but there was an

18. Hitzenberger, K.: Ueber Myotonische Dystrophie, Monatschr. f. Psychiat. u. Neurol. **47**:249 (May) 1920.

19. Brock, S., and Kay, W. E.: A Study of Unusual Endocrine Disturbances: Their Associated Myopathies, Endocrine Balance and Metabolic Findings, Arch. Int. Med. **27**:1 (Jan.) 1921. Janney, N. W. et al.: The Endocrine Origin of Progressive Muscular Dystrophy, ibid. **21**:188 (Feb.) 1918.

20. Boveri, quoted by Janney, Footnote 19.

21. VonWerdt, quoted by Janney, Footnote 19.

22. Hellmut-Maiweg: Progressive Muscular Dystrophy and Thyroid Hypoplasia, Ztschr. f. d. ges. Neurol. u. Psychiat. **63**:107, 1921.

increase in the chief and interacinal epithelial cells, which had so proliferated and accumulated that they were the principal characteristic of the sections (Fig. 6). There was also a marked increase in the mesoblastic structures, particularly in the vessel walls and in the stroma of the acini.

With the exception of a general increase in the stroma of the glands and a corresponding decrease in the parenchymatous tissues, I have not found special alterations in the pituitary or suprarenal glands; nor have

Fig. 5.—Thyroid gland from a case of progressive muscular dystrophy, showing excess of fibrohyaline tissue, thickened vessels, and very small, regressed acini, with an absence of colloid.

I had experience with the pineal and thymic cases discussed by Timme and others.

The material from cases with complete endocrine histories is not yet sufficient for an extensive research; histopathology has therefore contributed little toward the solution of the problem. Certainly the effects of the disease are not limited to muscle changes, but there still remains much to be accomplished in support of a theory that progressive muscular

dystrophy is a definite disease of the ductless glands, although many clinical features may result from the alteration in function of one or several glands.

THE GROUP OF HEREDITARY ATAXIAS

This group may be considered to contain the various forms of Friedreich's disease, spinocerebellar ataxia, cerebellar heredo-ataxia (Senator-Pierre Marie), Dana's hereditary spastic paraplegia and infantile progressive hypertrophic neuritis (Déjerine), and since the anatomic evidence points to an arrest in development of certain parts of the central nervous system with primary degenerations in the dorsal columns, the spinocerebellar and in the pyramidal tracts, the attention of practically all investigators has been directed toward the neuropathology. Several of these special forms of Friedreich's disease are exceedingly rare, and little is known of their pathology.

Fig. 6.—Thyroid gland from a case of amyotonia congenita. Note the abundance of interacinal epithelial cells, the irregular acini and the relative lack of colloid.

Regarding the extraneural systems of the body, there has been little mention except concerning certain deformities of the feet. A small heart [23] and an enlarged lymphatic system has been described in association with the disease. Necropsy material of this disease has not been available to me, but it is highly desirable that more general studies be made, since there are indications of an extraneural pathologic condition presented by some of the symptoms commonly found, such as polyuria, dyspnea, edema, diabetis, premature loss of hair and late appearance of the menses

THE GROUP OF HEREDITARY CHOREAS

While the principal pathologic changes have been found in the central nervous system, there are some extraneural pathologic features worth noting. This may also be true of the whole group of striatum syndromes, of which hereditary chorea is but a variant in the large picture.

In the cases of Huntington's chorea in which I have performed necropsies the usual gross lesions were found in the brain and its coverings, such as chronic inflammation of the dura with hematoma, chronic pia-arachnitis with adhesions and shrinkage of the brain convolutions. In addition, there was an advanced generalized arteriosclerosis, the effects of which were noted in all organs of the body. In fact, this marked tendency to arteriosclerosis with calcification developing earlier than would be expected was a characteristic feature.

The marked diffuse connective tissue increase throughout the body characteristic of the muscle dystrophies has not been found in the chorea group. Among the necropsy findings the most frequent lesions are: atheromatous aortitis, chronic interstitial myocarditis, hyperplasia of lymphatic systems, tuberculosis with tendencies to healing and calcification, chronic forms of nephritis, chronic passive congestion of the large glandular viscera and catarrhal conditions, with ulceration of the mucosa of the colon.

The thyroids exhibited calcium deposits in the vessel walls and in the tissue itself, and there was also a remarkable degree of interstitial fibrosis and a reduction of the colloid to one-third the usual amount. The pituitary gland usually appeared somewhat atrophied, and showed general interstitial connective tissue reactions microscopically, but in some cases there was little sclerosis of this gland.

The suprarenals in chorea usually show focal adenomatous enlargements of the cortex which is irregular in contour. In one case, there was a cortical adenoma the size of a walnut. The testes are not notably

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23. Pfeiffer, J. A. F.: A Case of Hereditary Ataxia (Friedreich's with Anatomic Findings, Arch. Neurol. & Psychiat. **7**:341 (March) 1922.

damaged, being in some cases particularly free from connective tissue changes, appearing in this respect like those of young men, with tubules and interstitial cells normal, and an abundance of spermatozoa.

THE GROUP OF MENTAL DEFECTIVES

In a group of 110 necropsies on the feebleminded, twenty-five were found free from gross brain defect and from clinical and laboratory signs of syphilis; so they were selected for this study in which special attention has been given to the circulatory system and to the histopathology of the endocrine glands.

Six of the twenty-five cases presented the status thymolymphaticus type of circulatory system with persistent thymus and enlarged lymphatic structures, and in addition the pituitary, thyroid, and suprarenals were slightly sclerotic. It is an interesting fact that four of these six cases during life exhibited well defined schizophrenic reactions in addition to the original mental defect.

Four cases exhibited the usual lesions of advanced subthyroidism, and both lobes of the thyroid were atrophied, pale and sclerotic, with the histologic picture of marked mesoblastic changes, colloid reductions, cystic degenerations, vascular alterations and lymphocytic infiltrations.

Five cases showed clinical and anatomopathologic features of hypopituitarism with an irregular patchy but dense increase in the interstitial connective tissue. The cell groups in these atrophied anterior lobes were universally small and composed chiefly of basophilic cells. More moderate scleroses with reduction in parenchymatous elements were found in the thyroid, suprarenals and gonads.

A fourth group composed of four individuals may be called the adrenogonadal group, since the main endocrine lesions were found in the suprarenal cortex and in the gonads. In the suprarenal cortex, the marginal groups of cell columns are often rudimentary and most frequently widely separated by densely organized connective tissue (Fig. 7), the cortex as a whole being quite narrow and aplastic, but frequently showing some areas of local hyperplasia of cells. The ovaries showed premature sclerosis and in the males the external genitalia were undersized, the testes exhibiting those changes usually described as regressive atrophy.

In six cases, the pituitaries, thyroids, suprarenals and gonads were universally affected in a manner suggesting diffuse polyglandular endosclerosis with a marked increase in supporting tissues and a deficiency in parenchymatous elements.

Definite aplasias and deformities of various organs are frequent findings in postmortem examinations on the feebleminded, and in the

foregoing types, aplasia of the kidneys and liver, bony deformities in the skull, vertebrae and feet and developmental peculiarities in the skin have been observed.

I have not had the opportunity to perform necropsies on cases of amaurotic family idiocy or on mongolian types. The published reports of the former deal mainly with the changes in the nervous system, and little has been done in glandular or other histology on the mongoloids,

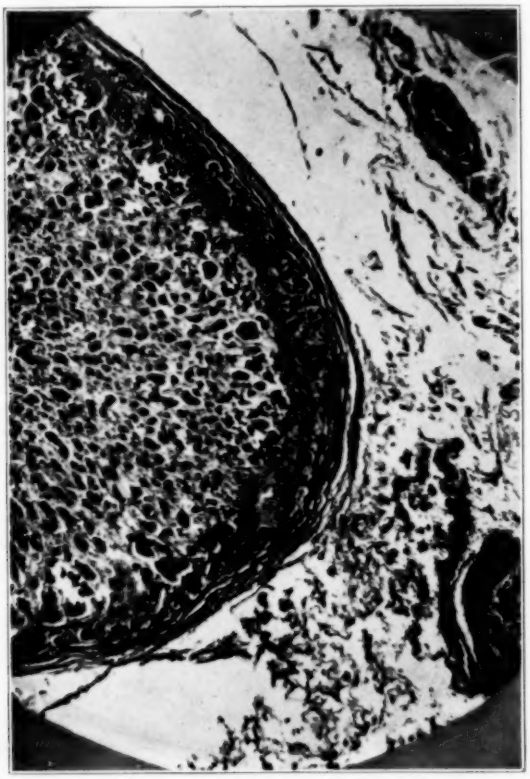

Fig. 7.—Low power magnification of a section of suprarenal gland from a case of imbecility, showing atrophic cell columns and dense sclerosis of the cortex, particularly of the marginal zone.

although, as Dr. Timme has pointed out, there is plenty of clinical evidence to indicate a glandular pathologic condition.

Structural growth and body characteristics are determined or at least influenced by the ductless glands, and since the time of Seguin, who in his original publication on idiocy mentioned pituitary and pineal atrophy, there have been a number of systematic attempts to study the relations between the endocrine glands and the mentally defective. In this con-

nection, interesting features have been reported by Swanberg and Haynes,[24] who studied the menstrual disturbances in 710 feebleminded females; by Potter,[25] who was able to arrange clinically over 300 cases into eleven definite and characteristic endocrine groups, and from the anatomopathologic standpoint by Raeder,[26] who noted changes in the endocrine glands in 74 per cent. in 100 necropsies.

It would seem that the feebleminded from original defect may be divided into (1) a neuro-ectodermal group characterized by developmental brain abnormalities and affecting secondarily the meso-entodermal and (2) a meso-entodermal group, involving particularly various endocrine integrators, and perhaps affecting secondarily the ectodermal derivatives including the nervous system, skin and appendages, etc.

THE EPILEPTIC GROUP

I shall give a summary of the pathologic features discovered in 215 necropsies performed at St. Elizabeth's Hospital—on all varieties of epilepsy. From these observations a monograph has been prepared on the neuropathologic features. In the present account, emphasis is placed on the extraneural systems.

1. From the standpoint of the circulatory system, the group may be divided into two main parts: those with a hypertrophied or diseased vascular system and those with aplastic circulatory features, which may or may not be associated with persistent thymus. The first mentioned is composed mainly of the "organic" types, while the latter is made up chiefly of the idiopathic regressive varieties, and those with additional dementia praecox developments. Of the total number, seventy cases were placed in the latter group.

On the basis of pathologic investigation, the hypoplastic types may be subgrouped as follows:

(*a*) The pancreatic insular and acinal sclerosis group (with or without persistent thymus). In these cases, the pancreas is found to be in various degrees of sclerosis; the islands are not always involved, and in some instances in which the islands are involved, the clinical notes do not indicate diabetes. Frequently, large bands of connective tissue radiate through the lobules of the gland. In my experience, pancreatic involvement with reduction in parenchymatous structures is one of the most frequent necropsy findings in epilepsy.

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24. Swanberg, H., and Haynes, H. A.: Menstrual Disturbance in the Feebleminded, J. Nerv. & Ment. Dis. **50**:224, 1919.

25. Potter, H. W.: Endocrine Imbalance and Mental Deficiency, J. Nerv. & Ment. Dis. **56**:334, 1922.

26. Raeder, O. J.: Endocrine Imbalance in Feebleminded, J. A. M. A. **75**:527 (Aug. 21) 1920.

(*b*) The anterior pituitary sclerosis group in which the principal chronic histopathologic change is in the anterior lobe of the pituitary in which the basophilic cells predominate, a patchy increase in the stroma obliterating fairly large areas of cell groups while the remaining ones are represented by small collections of cells (three or four cells to the group). In other areas, the cells react well to the stains. The pars intermedia is usually fibrous and contains few cell streaks.

(*c*) A third group, the pituitary-suprarenal-gonadal combination showing notable lesions in all three of these glands. The cell columns of the suprarenal cortex are irregular in size and distribution, and local scleroses alternating with whorls of compensatory hypertrophy are common. The gonads show various degrees of involvement, from a few focal obliterations to complete fibrosis of total gland substance (Fig. 8). In this group, the thyroid may also share the sclerosis with reduction of acini and fusion of epithelial cells.

The parathyroid glands have not been systematically examined.

THE DEMENTIA PRAECOX REACTION TYPES

During the past year, two publications have been made on the subject of constitutional factors in this group, and since then considerable material supporting the views therein expressed has accumulated in the author's laboratory.[27]

Briefly, the constitutional factors which are possibly inherited in the catatonic hebephrenic reaction are: (1) a larval status lymphaticus or an aplasia of the circulatory system, with hyperplasia of the lymphatics, which is predisposing to tuberculosis, and (2) inadequate tissue development or organization or "vitality" as shown by the regressive changes, atrophies and scleroses in the pituitary, thyroid and gonads, and by aplasia of the suprarenal cortex.

The foregoing point of view may be summarized by a quotation from the original text:

> The suggestion may be offered that it is just this type of inherited constitution, the inadequate, underdeveloped circulatory system and the deficient "tissue stuff" composing some of the endocrine glands, which renders an individual in danger of developing the "precox" psychosis at puberty or if there escaped at some subsequent period of more severe physical, chemical, psychic or social stress.

Patients with "paranoid" dementia praecox do not have this constitution, but these cases belong with the group of paranoid reactions.

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27. Lewis, N. D. C.: The Constitutional Factors in Dementia Precox. Nerv. & Ment. Dis. Monograph Ser. No. 35, New York and Washington, 1923. Lewis, N. D. C.: An Anatomical Study Contrasting the Dementia Precox Constitution with that of Paranoid Developments, South. M. J. **16**:327 (May) 1923.

THE PARANOID REACTION TYPES

An extensive monograph now ready for publication has been prepared from the investigations on the constitutional make-up of the compensatory reaction types, and the following conclusions are submitted from a study of the paranoid group.

The circulatory system is large, well developed and given to compensatory hypertrophy, and practically all patients die of circulatory

Fig. 8.—Testicle from a case of epilepsy showing complete fibrosis of tubules and interstitial structures.

accidents, such as ruptured aneurysm, cardiac rupture and decompensation and cerebral hemorrhages.

In addition to the marked tendencies and possibilities in hypertrophy and hyperplasia of the parenchymatous cells of many organs of the body, the endocrine glands show distinct changes, such as marked hypertrophy of the anterior pituitary cell groups, focal epithelial hyperplasias of the thyroid, focal cortical hyperplasias, often to a remarkable degree in the suprarenals, and combinations of focal atrophy, normal areas and focal hyperplasias in both tubules and interstitial cells of the testes.

SOMATIC PATHOLOGY OF MANIC-DEPRESSIVE MENTAL REACTIONS

Postmortem examination in these cases have frequently revealed various associated pathologic conditions of the nervous system and of the other organs, but in the past the field of somatic pathology has failed to contribute to the knowledge of the organism as a whole when affected by manic-depressive disorder. This failure is due to both the lack of systematic investigations in this field and to the fact that anatomopathologic material is difficult to interpret in this connection, since the psychosis is often a prolonged periodic process extending over many years, and the original tissue organization may thus be altered by senility and intercurrent diseases.

Owing to the prolonged and periodic character of the condition, suitable material available for postmortem study is limited; however, a number of clinically certain cases have been studied thoroughly, and from these studies one may attempt to draw some general conclusions as to the somatic construction of the manic-depressive type of person.

1. It is a well-known clinical observation that these patients are prone to develop surface infections particularly during the excited phases. Microscopic studies on the various tissues have emphasized the fact that numerous infections have occurred in the internal organs of the body during the life of the person. Small contracted healed areas are found more frequently than in the bodies of those affected by any other type of psychosis, and although they are not limited to any particular type of tissue, they are found more often in the thyroid, liver, lungs, kidneys and pancreas.

This finding would indicate that persons with cases of manic-depressive insanity are not only more prone to infections (lowered local resistance), but at the same time have tremendous reactive possibilities. However, the final outcome of 40 per cent. of manic-depressive constitutions is death from some form of acute septicemia, such as that from pyelonephritis, acute suppurative cholecystitis and streptococcic septicemia, while only 10 per cent. of the patients whose cases were studied by the author died of pulmonary tuberculosis.

2. The circulatory system in general is large and compensates easily for extra strain; however, death from circulatory accident, such as cerebral thrombosis, subdural hematomas, cerebral hemorrhages and cardiac decompensation, occurs in about 50 per cent. of cases. In this respect, the manic-depressive shares many features with the paranoid types.

Generalized arteriosclerosis with associated tendencies to infarction of various organs, kidney disorders, venous thromboses and miliary hemorrhages is more often encountered in the aged person with manic-depressive psychosis than in the average senile person.

3. The endocrine glands exhibit peculiar combinations of atrophies, hypertrophies and hyperplasias.

In a number of cases, the pituitary gland has been found grossly atrophied, occasionally to an extreme degree. Microscopic examination of these glands discloses a tendency on the part of individual cell groups to compensate by hyperplasia, and in a few instances, typical local adenomas have developed in the anterior lobe. The posterior lobe is usually in a state of fibrous atrophy.

The thyroid glands exhibit the scars (frequently calcified) of numerous previous infections, which have probably developed secondarily from throat or tonsillar infection, etc. In some cases, there is fibrous atrophy of the gland as a whole, but more often the epithelial cells attempt to reconstruct the parenchyma, and thus secondary hypertrophies arise. Miliary hemorrhages may be numerous through the interacinal stroma.

The suprarenals generally exhibit cortical hyperplasia, but not to the remarkable degree noted in the paranoid types; however, there is a tendency to general atrophy of both cortex and medulla, and moderate local attempts at reconstruction on the part of the cortex. Miliary hemorrhages into the substance of the suprarenals are often found.

The gonads are well preserved as a rule; even in senile cases there may be less atrophy than expected. The testes in an occasional case may show some diffuse atrophy of both tubules and interstitial cells and reduction in the spermatogenic function, while in other instances focal destructions have occurred either from vascular involvement or previous infective invasions.

DISCUSSION AND CONCLUSIONS

1. For purposes of review and reference, it may be well to emphasize that primitive embryonic cells are similar in structure, and each possesses the basic properties of reproduction, irritability, contractility and metabolic activity. These primitive cells carrying the hereditary factors gradually differentiate, by the process called histogenesis, into groups of more specialized tissue cells with a structure and function specifically adapted through evolution to maintain a certain position in the division of labor of the organism.

The hereditary defect in the germ plasm through the process of primitive cell proliferation and division, must be distributed to one or to more than one of the early germ layers, there to affect the growth, development or vitality of some or all of the organs developing therefrom.

2. Authorities are yet undecided as to whether these so-called hereditary and familial conditions result from arrest or alteration in development of some part of the central nervous system, an inherited defect in the muscle spindles in the case of the progressive muscular disorders, or

to primary disease of the endocrine glands. Since abnormal skeletal growth, abnormal quantity and distribution of hair, obesity, diabetes, goiter and fatigue states, vasomotor disturbances, alterations in spacing of teeth and invert signs of secondary sex characteristics, such as breasts in the male, mustache and male pubic hair in the female, etc., are frequent findings in the "hereditary" disorders, and at the same time are well recognized clinical manifestations of endocrine disturbance, many investigators have emphasized the possibility of primary factors in the endocrine organization.

3. Combinations of and transition forms between progressive muscular dystrophy, family spastic paraplegia, Friedreich's disease and the hereditary choreas have been described, and since any of these may be found associated with mental deficiency, the epilepsies and some psychoses, there is justification for the creation of an hypothesis which will attempt to account for the production of the pathologic processes by supposing the presence of a defective basic factor operating or focusing in one or another of the early germ layers.

4. The focus of operation of this factor in the hereditary choreas is apparently in the striatum areas, while in the hereditary ataxias it is more definitely in different levels of the primitive neuro-ectodermal structures. In true Friedreich's disease (spinal heredo-ataxia), the defect appears as a hypoplasia of the spinal cord with arrest of development of the posterior columns, direct cerebellar tracts and lateral pyramidal tracts; in Marie's ataxia (cerebellar heredo-ataxia), cerebellar maldevelopment is characteristic, while in the infantile progressive hypertrophic neuritic form of Déjerine, the peripheral nerves exhibit the defect. The blending of these types suggests a unitary causative factor which acts primarily in any one of several levels and which produces not only the characteristic pathology of that region, but creates secondary changes as well in the mesoderm and entoderm in the form of vascular and endocrine gland alterations, bony deformities, and diffuse overproductions of connective tissues.

Kollorits has reported a combination of Huntington's chorea and Friedreich's ataxia, and Bing has described a case of hereditary ataxia in which there was also progressive muscular atrophy; moreover, if a complete classification such as that of Jendrassik is studied, it will be seen that the activity of the defective factor may be traced through transition forms to the progressive muscular dystrophies. Here the derivatives of the mesoderm show severe alterations in the form of muscle, bone and endocrine lesions, tremendous overproductions of connective tissues and frequently secondary changes in the ectodermal and entodermal derivatives.

5. There is much overlapping of clinical and anatomic pictures among the feebleminded, epileptic, dementia praecox, paranoid and manic-depressive groups, and many features are identical; moreover, epilepsy and feeblemindedness show a great similarity in their hereditary reaction, both appearing to be due to a defect in the germ plasm. They are both recessives, and are frequently found associated. The patient with genuine epilepsy usually comes from a badly tainted stock, which, if free from epilepsy itself, nevertheless, shows other nervous disorders, such as chorea, migraine, etc. (Weeks).

The defective factor in the epileptic and feebleminded groups is located primarily in some instances in the central nervous system (neuro-ectoderm layer) and produces secondary alterations in the mesodermal and entodermal differentiated structures, while in other groups of these cases there is no demonstrable primary alteration in the central nervous system, but the vascular and glandular tissues show aplasias or other advanced lesions, as may also the glandular derivatives of the entoderm, which are sufficient to account for the defects, the metabolic imbalance and the inadequate integration of the organism as a whole.

It is obvious from the hereditary standpoint of the psychoses, that our classifications must be extremely elastic, as Bleuler has well emphasized in his criticism of Rüden's study of heredity in dementia praecox. He points out the rigidity in Rüden's formulation of dementia praecox which fails to include many larvated or undeveloped cases that never get into institutions—"many who never develop a characteristic schizophrenic picture or remain well under exceptional favorable circumstances, but all of whom may be the bearers of a germ plasm factor of praecox significance" (White).

Neuropathologic studies of the central nervous system in cases of praecox, paranoia and manic-depressive types have failed in the past to disclose any lesions which may not be interpreted as secondary in nature, that is, produced by general metabolic disturbances or by intercurrent diseases. There is, however, considerable evidence made available by careful study of the mesodermal and entodermal structures that the disturbance in integration in these disorders lies in the development of defective tissue stuff outside the neuro-ectoderm with each of the aforementioned psychoses exhibiting anatomopathologic features in a general way characteristic of its type, but occasionally showing an admixture of tissue tendencies. In short, it may be stated that the constitutional characteristics of the mental groups indicate that the focus of primary alteration is probably located in those primitive cells the later differentiation of which produces the mesodermal and ectodermal structures. The factor or factors inherited may represent a general instability of integration (regression or overcompensation) with varying degrees of resistance to the environmental load.

SUGGESTIONS FOR FUTURE RESEARCH

(*a*) A general histopathologic investigation of the early minute changes in the muscle spindles could be carried out with profit on the infantile forms, and a more careful study of the smooth muscle structures, particularly of the gastro-intestinal tract, in all cases of muscular dystrophy coming to necropsy would be of considerable value in determining the extent of the muscular involvement.

(*b*) A correlative clinical and anatomic study of the basal ganglia, the parathyroid gland and the general vascular alterations in cases of hereditary and other choreas might add materially to the knowledge of the etiology of the disorder.

(*c*) The frequence, degree and character of the various organ aplasias should be considered in connection with the behavior of the personality in a more comprehensive and systematic manner, since these aplasias (using the term in its restricted sense) are probably inherited and often indicate a markedly defective function. Such an investigation should include not only parts of the central nervous system, but also the extraneural systems of the body, and more particularly the circulatory organs and the endocrine glands.

HYPOPHYSIAL PRESSURE SYMPTOMS DUE TO HYDROCEPHALUS CAUSING CYSTLIKE DISTENTION OF THE THIRD VENTRICLE*

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PHILADELPHIA

Hypophysial symptoms may be caused by several pathologic states, and consequently may present diagnostic difficulties. Such symptoms may arise from causes within or without the hypophysis. In the latter case, hydrocephalus may cause disturbances of the function of the hypophysis itself, with or without evidences of pressure on the olfactory and optic nerves, or may cause cerebellar symptoms, or disordered function of the pons, in all of which conditions structural changes in the sella turcica may or may not be present. What causes the hypophysial symptoms, and how differentiate cases in which the primary lesion is in the region of the hypophysis or is distant from this organ?

The cases bearing on this problem may be divided into: (1) those in which there is idiopathic hydrocephalus causing cystlike deformity of the third ventricle or distention elsewhere, and secondary to this, the symptoms of pressure in the region of the sella turcica or cerebellum; (2) those cases of cerebellar tumor which give rise to hydrocephalus which in itself causes hypophysial symptoms due to dilatation of the third ventricle, masking the symptoms of cerebellar tumor, and (3) cases of suprasellar tumor which may cause (*a*) hypophysial symptoms or (*b*) cerebellar symptoms. The case here reported illustrates some of the difficulties of this problem and suggests diagnostic signs possibly of importance.

REPORT OF A CASE

History.—The patient was a mentally deficient boy, aged 18, who was admitted to the Polyclinic Hospital, Oct. 13, 1922. The family history was negative. He had had influenza and pneumonia in 1918, and sunstroke when 5 years of age. He had never advanced beyond the third grade in school, but otherwise apparently had been perfectly well and healthy. Two years previously, his vision had begun to fail, and he became completely blind in February, 1922.

Examination.—He was a large, fat boy. The growth of hair was profuse, and the pubic hair masculine; there was no hypoplasia of the genitalia. The anteroposterior diameter of the head was greater than the lateral diameter.

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* Read at the Fifth Annual Meeting of the American Neurological Association, Philadelphia, June 7, 1924.

There was no facial paralysis; ocular movements were normal; the tongue protruded in the median line; the masseter muscles contracted equally well on both sides. There was no paralysis of the limbs. Abdominal and cremasteric reflexes were active; the arm reflexes were diminished; the knee reflexes were equal and increased; the Achilles reflexes were exaggerated; bilateral persistent ankle clonus was present; Oppenheim and Babinski reflexes were absent. The sense of smell was diminished on the left side. The dynamometer on the left was 35, on the right, 45. Although the Romberg sign was absent with the feet together or even slightly separated, a slight push on the chest would cause him to fall backwards. After admission to the hospital he had two or three slight general convulsions. Apparently, he was conscious in these, and the attacks were followed by headache and eye ache.

The urine was normal. Red blood cells, leukocytes and hemoglobin were normal, and the Wassermann reaction was negative. The cerebrospinal fluid showed 2 cells per cubic millimeter, negative Wassermann, protein, globulin and sugar reactions, and the colloidal gold curve was 1112221000.

Sugar tolerance was diminished, as follows: 0—87 mg. per 100 c.c.; 1—210 mg. per 100 c.c.; 2—142 mg. per 100 c.c.; 3—110 mg. per 100 c.c. The blood chemistry showed no abnormalities, and the basal metabolism rate was —11.

Roentgen-Ray Examination.—The roentgenogram showed enlargement of the sella turcica which measured approximately 16 mm. in length and 17 mm. in depth. The floor of the sella was very thin. The posterior clinoid processes were destroyed, and the anterior clinoid processes pushed forward and upward and very thin. There was no evidence of invasion of the bone of the floor of the sella nor of the anterior clinoid processes, such as would be produced in a malignant growth. The general appearance indicated a pressure effect, and the pressure evidently came from behind forward, thereby destroying the posterior clinoid processes and pushing forward the anterior clinoid processes.

A roentgen-ray examination of the sinuses was made, but aside from the fact that the frontal sinuses on the left were not seen and on the right were small, no disease was found. Dr. Ralph Butler reported that there was slight deflection of the septum to the left and a thick discharge on both sides. The blood vessels were enlarged on the right side of the septum, the tonsils hypertrophied and submerged, and pus could be expressed from them.

Eye Examination.—The eye examination by Dr. Luther C. Peters revealed large, equal and regular pupils, which did not respond to light. On the right side, the media were clear, the disk pale, white, and infiltrated, with the margin very much blurred. The arteries were small and contracted; the macular twigs very tortuous and in some places twisted like a knot in a rope. Marked perivasculitis was present. On the left side the disk was chalky white and the edge obliterated. The vessels were lost in this white exudate, and the veins, very small, ropelike and tortuous, were completely obliterated in places, other areas appearing as mere white lines. The large arteries were the seat of advanced perivasculitis. There were numerous atrophic areas visible in the retina. The diagnosis was atrophy secondary to a neuroretinitis. There had possibly been a choked disk at some time, on the left, and the primary condition was undoubtedly violently inflammatory.

Examination made by Dr. Walter Roberts revealed nerve deafness on the right. The Bárány test by Dr. Lewis Fisher indicated pressure on the fourth ventricle, probably from some cerebellar involvement.

Operation and Course.—Dr. Grant attempted a transphenoidal hypophysectomy, on Dec. 27, 1922. After considerable difficulty, the nasal septum was

removed, until the prow of the vomer was seen. This was removed, and the sphenoid cells identified and entered when the anesthetist reported the patient was in poor condition. For this reason, the wound was closed and the patient returned to the ward. He died ten hours later.

Necropsy.—Necropsy was performed by Dr. Grant. He reported: "The calvarium was removed without difficulty. There were no adhesions between the brain and membranes. On removal, the brain showed what was apparently a large suprachiasmal cyst, which proved to be a much dilated third ventricle.

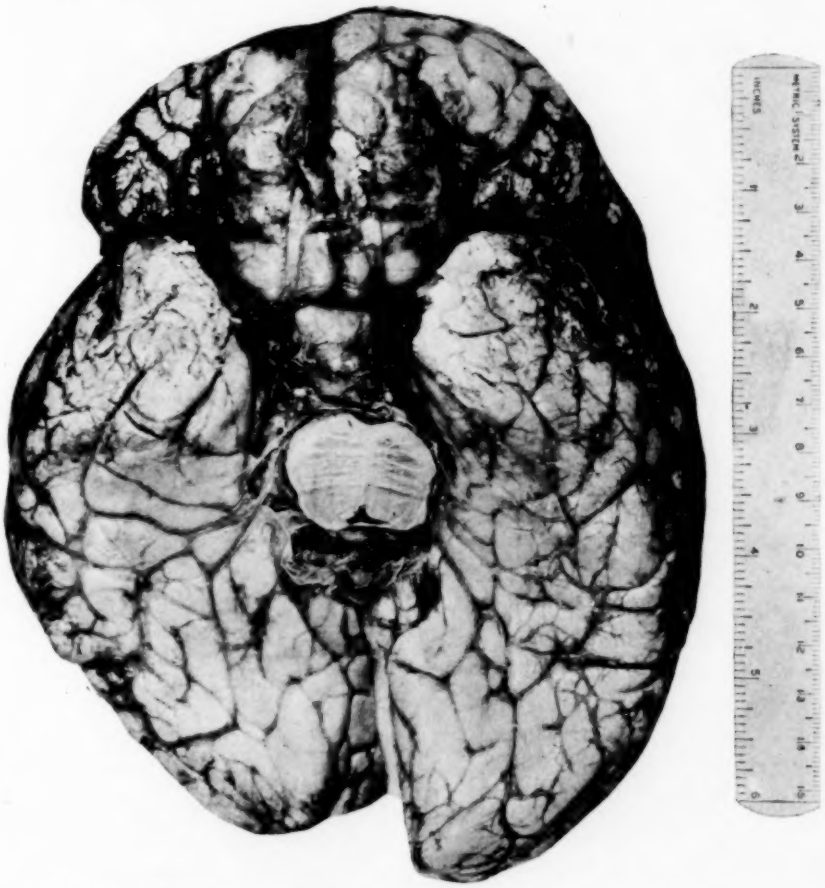

Fig. 1.—Dilated third ventricle and the vestiges of the optic chiasm.

There was marked symmetrical dilatation of both lateral ventricles. The sella turcica was much enlarged, and both anterior and posterior clinoid processes were destroyed. The pituitary body was pushed downward and forward and was flattened out against the dorsum sellae by the dilated third ventricle. The pituitary fossa was about 17 mm. deep. The operative approach had reached the sphenoid cells but had not passed through the floor of the sella."

Examination of the brain by Dr. E. A. Case showed that the convolutions were flattened and the sulci narrowed. Both lateral ventricles were enormously

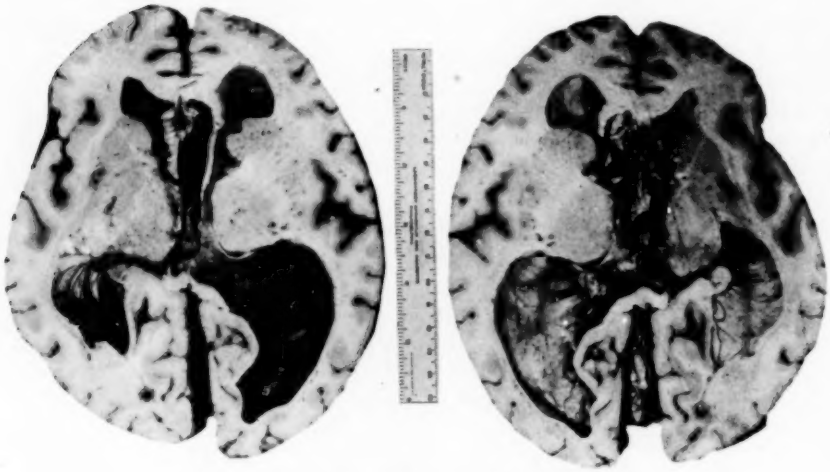

Fig. 2.—Marked dilatation of the ventricles.

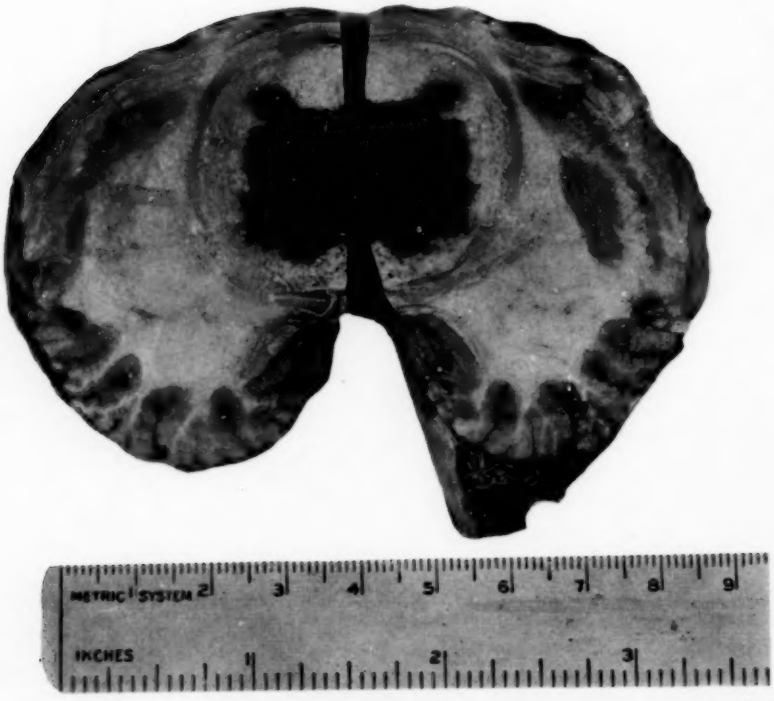

Fig. 3.—The cerebellar tumor.

distended. The third ventricle had been transformed into a sac which projected downward as a rounded mass in front of the pons, measuring 2 cm. in diameter and 2.5 cm. in depth. It had crowded the structures in this region causing pressure atrophy, the only trace of the optic chiasm being the two stumps of the optic nerves which projected from its rounded extremity and a ribbon-like vestige of the optic chiasm. The fourth ventricle was also much distended. The right cerebellar hemisphere was about one fourth larger than the left, and extended almost 1 cm. beyond the median line. On the under surface of this hemisphere, there was a discolored area of irregular outline, measuring 2.5 cm. in its greatest diameter. Section of this hemisphere showed a fairly well circumscribed variegated appearing tumor, occupying almost the entire thickness of the cerebellum at this point. It measured 3 by 3 by 2 cm., was hemorrhagic, slightly softer than the surrounding tissue, marked with dark red, grayish and small translucent areas, and at the periphery there were minute colliquation cysts. Microscopically, the cells were elongated and had elliptical nuclei which stained well with hematoxylin. Between the cells and forming a network in which they lay, numerous strands of glia fibrils were seen, showing well when stained with Mallory's phosphotungstic acid-hematoxylin. By careful examination, many of the fibrils could be traced to the cells from which they seemed to spring. The cells and fibrils formed no geometric pattern.

COMMENT

The outstanding symptoms in this case were a moderate degree of adiposity, lowered sugar tolerance, anosmia, epileptiform convulsions and secondary atrophy of the optic nerve, with roentgen-ray demonstration of partial destruction of the anterior and posterior clinoid processes, and deepening and distortion of the sella turcica. The only symptom suggestive of cerebellar tumor was the inconstant tendency to fall backward.

In 1918, I [1] reported a case of hydrocephalus exhibiting cerebellar symptoms, in which there were two cystic dilatations of the lateral recesses of the fourth ventricle, situated at the cerebellopontile angle. The cerebrospinal fluid had apparently forced the arachnoid and pia out in such a manner as to give the appearance of a cyst on each side. In a case cited by Spiller,[2] which presented cerebellar symptoms, all the ventricles were dilated. Virchow [3] had previously described a case in which the fourth ventricle was partially dilated, giving rise to a cherry-sized cyst between the cord and the cerebellum. Von Recklinghausen [4] reported a case in which there was a bilateral cyst which communicated with the dilated fourth ventricle. In Oppenheim's [5] case, there was bilateral optic atrophy, optic neuritis, contracture of the

1. Rhein, J. H. W.: Cerebellar Symptoms in Hydrocephalus, J. A. M. A. **51**:1933 (Dec. 5) 1908.
2. Spiller: Am. J. M. Sc. **124**:44, 1902.
3. Virchow, in Scholz: Path. des Tumeurs, p. 180, 1867.
4. Von Reckinghausen: Virchows Arch. f. path. Anat., 1864, No. 30.
5. Oppenheim: Monatschr. f. Psychiat. u. Neurol. **18**:221, 1905.

sternocleido-mastoid and trapezius muscles, weakness of the left leg, a right-sided Babinski sign, increased patellar reflexes and weakness of the lower left facial muscles. A diagnosis of cerebellar tumor was made, but at necropsy only internal hydrocephalus was found. The second case cited by Oppenheim showed cerebellar symptoms, and at necropsy the only pathology was hydrocephalus internus. Finklenburg cited a case in which the symptoms were those of cerebellar tumor, and necropsy showed dilatation of all the ventricles, with marked bulging of the infundibulun.

Furthermore, cystlike formation occurs in hydrocephalus as the result of distention of the third ventricle. The hydrocephalus may be of the idiopathic type or secondary to a neoplasm. Pressure from the dilated third ventricle causes more or less extensive changes in the sella turcica and also alterations in the functions of the hypophysis. There is a fairly large number of cases now on record which illustrate this condition. Schüller [6] cited a case in which there was increased brain pressure and widening of the sella turcica, but no increase in the size of the hypophysis. Fürnrohr [7] has seen widening of the sella turcica in similar conditions, and Oppenheim [8] called attention to changes in the sella turcica due to dilatation of the third ventricle which caused pressure on the optic and abducens nerves. In a case reported by Strauch,[9] there was pressure on the hypophysis, the symptoms being supra-orbital headaches, polydypsia, polyuria, adiposity and increased sugar tolerance. Necropsy revealed marked hydrocephalus, large shallow sella and clinoid processes worn away. As a result of this pressure, some actual changes had taken place in the hypophysis. In the case recently reported by Friedman [10] in which there were cerebellar and hypophysial symptoms in a girl, aged 22, necropsy revealed a dilated third ventricle compressing the hypophysis and causing enlargement and erosion of the sella turcica. In Schultz' [11] case, a diagnosis of hypophysial tumor was made in a patient, aged 18, who showed hypoplasia of the genital organs and in which hydrocephalus only was found. Stumpf [12] cited two cases in which hydrocephalus was associated with disturbances of function of the pituitary gland. In these cases, the sella turcica was not enlarged. He called particular attention to the fact that pressure on the sella by a distended third ventricle affected the anterior portion of the

6. Schüller, in Goldstein, Kurt: Arch. f. Psychiat. **47**:125, 1910.
7. Fürnrohr, in Goldstein, Kurt: Arch. f. Psychiat. **47**:125, 1910.
8. Oppenheim, in Pollock: J. A. M. A. **64**:395 (Jan. 30) 1915.
9. Strauch, A.: Hypophysial Dystrophy in Hydrocephalus, J. A. M. A. **72**:1731 (June 14) 1919.
10. Friedman: J. Nerv. & Ment. Dis. **59**:489, 1924.
11. Schultz: Deutsch. med. Wchnschr. **49**:1072, 1923.
12. Stumpf: Virchow's Arch. f. path. Anat. **219**:339, 1912.

hypophysis, and that even with strong pressure there was little or no change in the histologic structure of the pituitary gland. He further noted that genital hypoplasia and adiposity may be associated with chronic hydrocephalus without dilatation of the sella and without pronounced implication of the pituitary gland. Cushing [13] has reported a case of adiposity and lowered metabolism, the result of flattening of the hypophysis by a distended third ventricle, and two other cases in which the third ventricle was distended, in one secondary to a cerebellar cyst and in the second to a neoplasm in the right hemisphere. Pollock [14] has recorded two cases of distention of the third venticle as the result of hydrocephalus, which gave rise to hypopituitarism. In one of the cases, the roentgen ray showed a normal sella. Marinesco and Goldstein [15] reported two cases of hydrocephalus with adiposity, in one of which there was a cystic tumor and in the other a normal and small hypophysis. Kurt Goldstein [16] has also noted changes in the sella accompanying hydrocephalus.

The case reported in this paper is especially interesting as illustrating the difficulty in the diagnosis of cerebral or cerebellar lesions which give rise to hydrocephalus, itself causing symptoms which overshadow those due to the neoplasm itself. When cerebellar symptoms occur in tumors in the region of the hypophysis, the diagnosis is still more difficult. Percival Bailey [17] has reported three illustrative cases in which suprasellar tumor caused cerebellar symptoms. In two of them, there was choked disk, and in two the symptoms were such as to lead to a cerebellar exploration. The cerebellar symptoms developed late in the course of the disease. Cerebellar tumors usually produce cerebellar disturbance from the first. He states that according to Claude Vincent disturbances of equilibrium due to lesions in the cerebellum are due to disturbances of the functions of the cerebellum, such as hypotonicity, hypermetria and tremor, while those which are the result of hypertension arise from disturbances of the vestibular apparatus.

An additional symptom of diagnostic significance in my case was anosmia. To this symptom attention has not frequently been called. Cushing [18] reported two cases bearing on this subject. In his cases, pressure was exercised on the olfactory nerves by herniation of the brain

13. Cushing: Pituitary Body and Its Disorders, Lippincott Company, 1912, p. 202.

14. Pollock, L. J.: Hypopituitarism in Chronic Hydrocephalus, J. A. M. A. **54**:395 (Jan. 30) 1915.

15. Marinesco and Goldstein: Nouv. Iconog. de la Salpêtrière **22**:628, 1909.

16. Goldstein, Kurt: Arch. f. Psychiat. **47**:125, 1910.

17. Bailey, Percival: Concerning the Cerebellar Symptoms Produced by Suprasellar Tumors, ARCH. NEUROL. & PSYCHIAT. **11**:137 (Feb.) 1924.

18. Cushing: J. Nerv. & Ment. Dis. **44**:415, 1916.

structure into the interclinoid space. Oppenheim [19] had already referred to implication of the olfactory tracts in instances of dilatation of the third ventricle. Quix [20] quotes Musken who examined the olfactory sense in fifteen cases of increased intracranial pressure. He found that large tumors in the posterior fossa caused more disturbance of smell than those in any other region. He believed that implication of this function was due to that which increased intracranial pressure. Quix also quoted Quincke and Oppenheim, who have demonstrated atrophy of the olfactory nerve as the result of increased intracranial pressure in a tumor of the cerebellum. Gray [21] reported four cases in a series of sixty-one subtentorial tumors in which the sense of smell was impaired, in all of which there was increased intracranial pressure.

In cases of hydrocephalus in which the cerebellar symptoms are pronounced, there seems to be no positive way of differentiating them from cerebellar tumor. Finkelburg,[22] in discussing the diagnosis between cerebellar tumor and chronic hydrocephalus, states that cerebellar gait is an early symptom in both chronic hydrocephalus and tumors of the central ganglia, that lowered reflexes do not rule out chronic hydrocephalus, that Schmidt's symptom was found in both conditions, and that circumscribed tenderness to pressure and percussion is found in chronic hydrocephalus as well as in cerebellar tumor. Schmidt believed that the Westphal phenomenon indicates a tumor rather than idiopathic hydrocephalus. Severe unilateral choked disk points rather strongly to a one-sided lesion in the cerebellum.

In the roentgen-ray findings, I believe an important indication is the character of the deformation of the sella. The pronounced alterations in the shape and size of the sella in my case seemed to indicate a destructive process in this region, hence the operation. In what way can the character of the pressure causing the changes in the sella be determined? The reading of the roentgenograms by Dr. Pfahler throws some light on this question. It indicated that the pressure which brought about the changes in the sella came from behind, eroding or destroying the dorsum sellae, pushing upward and forward the anterior clinoid processes, and deepening and enlarging the sella itself. If the roentgenogram shows this type of deformity, it should at least suggest that it was the result of gradual diffuse pressure from a distended third ventricle. This may be regarded as an important diagnostic sign.

The character of the eyeground and visual field changes has some value in differentiating between cerebellar symptoms due to tumor and cerebellar and hypophysial symptoms due to hydrocephalus. When a

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19. Oppenheim: Text Book of Nervous Diseases, Chicago, Chicago Medical Book Co. **2**: 1911.

20. Quix, in Lewandowsky: Handbuch der Neurologie **2**:977, 1910.

21. Gray: Bull. Johns Hopkins Hosp. **36**:251, 1916.

22. Finkelburg: Deutsch. Ztschr. f. Nervenh. **29**:135, 1905.

patient is seen early enough to study the visual fields, in the absence of choked disk the characteristic cutting of the fields due to pressure on the chiasm from a lesion in the region of the hypophysis is of diagnostic value. It is well known that in most instances lesions in this locality do not cause choked disk but rather field changes followed by simple atrophy of the optic nerve.

Patients with cases like those under discussion often present themselves for the first time with complete blindness, the optic atrophy being of secondary type. The presumption would be in favor of regarding a case which showed a secondary optic atrophy on an inflammatory basis as being due to a cerebral or cerebellar lesion, or at least it should raise some doubt that the lesion is purely one in the region of the hypophysis.

DISCUSSION

DR. HARVEY CUSHING, Boston: Was the patient blind?

DR. JOHN H. W. RHEIN, Philadelphia: Yes.

DR. CUSHING: This fact of course served to exclude what is possibly the most dependable clinical test that one can have in a case of this kind. In other words, carefully conducted perimetric observations, if made before blindness came on, would probably have shown whether the tumor occupied the suprasellar region. I am glad that Dr. Rhein has reported this case, although it concerns a matter familiar to neurosurgeons, probably all of whom at one time or another have made mistakes of this kind. Many of us have already said something on the subject in print, but these warnings are apt to be lost.

To distinguish between a lesion in the region of the midbrain which deforms the sella by direct pressure and a lesion situated in the posterior fossa, which almost as quickly deforms the sella as a result of an internal hydrocephalus, is one of the difficult differentiations to make. It is something, furthermore, of which we have long since learned to beware. Certainly, no one trained in neurosurgery would ever venture to perform a transphenoidal operation when there is any doubt. When in doubt, one might be led to explore the region of the third ventricle by an osteoplastic craniotomy, but certainly not by a transphenoidal operation.

So far as I can see, this case seemed to be symptomatically one of cerebellar tumor from the beginning, although I admit that it is easier to make a diagnosis of a cerebellar tumor from symptoms after the results of the necropsy are known. The lesson in this case should be emphasized: namely, that a cerebellar tumor in a young person quickly alters the outlines of the sella, and one must not depend on those outlines for a localizing diagnosis.

Another fact is perhaps worth bearing in mind: A suprasellar tumor in a child that might cause an internal hydrocephalus from occlusion of the foramen of Monro is apt to have calcareous depositions that are shown in the roentgenogram; also, an ordinary adenoma is not only rare in a child, and even in an adult rarely produces an internal hydrocephalus.

I may say also that I think Dr. Rhein's title is an unfortunate one; for so far as I can see, this is *not a cyst* of the third ventricle—it is *merely a dilatation* of the third ventricle, which is an inevitable accompaniment of internal hydrocephalus, and which sometimes may so balloon the third ventricle as to give the appearance of a cyst from below.

TRYPARSAMIDE IN SYPHILIS OF THE NERVOUS SYSTEM

PRELIMINARY REPORT *

SIDNEY I. SCHWAB, M.D.
AND
LEE D. CADY, M.D.
ST. LOUIS

A brief account of the use of tryparsamide in the neurologic service at the Barnes Hospital may be of use in helping to appreciate at their proper value the reports of other clinicians. Chemically, tryparsamide is derived from atoxyl, which was one of the combinations in the arsenical series finally leading up to arsphenamin. It is a pentavalent arsenical. It was found to be effective in the treatment of experimental syphilis and trypanosomiasis, but it was discarded as far as human syphilis was concerned on account of the directly detrimental effect on the optic nerve. There is therefore little to be learned from the early use of atoxyl, except reports dealing with high percentages of visual complications. The same was true of the next pentavalent arsenical—arsacetin.

Working with these two drugs, Jacobs and Heidelberger, in 1905, made a substance, N-phenylglycinamide-p-arsonic acid, which was biologically studied by Wade Brown and associates of the Rockefeller Institute. Its sodium salt was given the name of tryparsamide, because it was found to be of great therapeutic activity in experimental and human trypanosomiasis—the tropical sleeping sickness. Its use in human syphilis was not seriously considered at that time, because the earlier experiments on human primary syphilis were found to be ineffective. Lorenz and Loevenhart, at the suggestion of Wade Brown, began the study of syphilis of the nervous system, and their publication is the first evidence in the literature that this drug had any place in the therapy of syphilis. Tryparsamide is a pentavalent arsenical belonging structurally to a group in which all appear to have an affinity for the optic nerves. As will appear later, this predilection seems less direct than the two others to which reference has been made.

PREVIOUS LITERATURE

There are four important papers in the literature up to the present time and one or two brief notices. A paper by Lorenz and Loevenhart [1]

* Read at the Fiftieth Annual Meeting of the American Neurological Association, Philadelphia, June, 1924.

1. Lorenz, W. F.; Loevenhart, A. S.; Bleckwenn, W. J., and Hodges, F. J.: The Therapeutic Use of Tryparsamide in Neurosyphilis, J. A. M. A. **80**:1497 (May 26) 1923.

dealing with a large amount of material, mainly from institutional cases; one by Keidel and Moore,[2] dealing with a series of neurosyphilitic cases from the dermatologic dispensary of Johns Hopkins; an authentic review of tryparsamide, chiefly in its biologic and pharmacologic aspects, by Brown and Pearce;[3] and a fourth paper by Young and Loevenhart which has recently appeared in *The Journal of Pharmacology and Experimental Therapeutics.*

Brief quotations from the literature are pertinent to the understanding and interpretation of the results obtained in the series of cases here described. Tryparsamide was first used in induced syphilis in rabbits and monkeys, and was found to be of great promise. Its toxicity and the changes produced in vision were experimentally studied. Its activity in animals infected with tryparsamide was remarkable. Its effect on syphilis in animals was unusual, especially when it came to be known that its spirocheticidal activity was almost nil. Experiments on animal resistance to spirocheticidal infection and the effect of tryparsamide in increasing it lead to the important conclusion that this drug chemically increases in animals, not only resistance to the infection, but the cellular defense reaction as well. It is on this principle that tryparsamide is used therapeutically. It does not kill nor inhibit the growth of the organism of syphilis, but it makes possible a successful defense on the part of the organism. In animals (rabbits), changes produced by tryparsamide in the retina are not identical with those found in the human being. The former appear to be incapable of resolution; the latter disappear when the drug is given up, and as a rule do not appear when treatment is resumed. It was found that the essential factor of the arsenicals in the production of optic changes was not the valency but the presence of an amino group in the compound.

THE USE OF TRYPARSAMIDE

In October, 1923, the Rockefeller Institute sent enough tryparsamide to the neurologic service of the Barnes Hospital for about fifty cases of neurosyphilis. Since then a larger amount has been at our disposal. Treatment was begun as soon as our material could be properly sifted; the present report deals with about ninety-seven cases. In the series is included practically every type of syphilis of the nervous system, with tabes and general paralysis, or their combinations, in preponderance. Cases in which optic atrophy was found or in which this was the prominent symptom or finding were also included, although at first such patients were not treated. In the early group of cases, selection

2. Moore, J. E.; Robinson, H. M., and Keidel, Albert: Tryparsamide in the Treatment of Syphilis, J. A. M. A. **82**:528 (Feb. 16) 1924.

3. Brown, Wade H., and Pearce, Louise: Tryparsamide: Its Action and Use, J. A. M. A. **82**:5 (Jan. 5) 1924.

was made largely on the basis of previously long and ineffective treatment and on the basis of chronicity and hopeless outlook. This was soon given up, however, and cases of neurosyphilis as they presented themselves were considered from the standpoint of tryparsamide therapy. As familiarity with the visual changes produced was obtained, cases in which optic atrophy was present were included. Acute retinal changes due to syphilis, or the presence of marked optic neuritis, was considered sufficient reason for exclusion, although there have been one or two instances later in this series in which definite changes of this kind were found and ignored. An unusually large number of cases are diagnosed as general paralysis, and it is interesting to note that in Lorenz and Loevenhart's material a similar difficulty in regard to the diagnosis of general paralysis is mentioned. A certain percentage of cases are noted in which mental changes have occurred, and if neurologic and serologic evidence is commonly associated with general paralysis, it seems fair to conclude that such patients are either showing a paretic reaction or are on the way to such a reaction. Such cases are grouped temporarily at least in this series under the group of general paralysis. It is obvious that a complete revision of the term general paralysis must soon be made. The term general paralysis should imply a clinical picture and a pathologic process and should not necessarily be limited to behavior or conduct anomalies which preclude an individual from maintaining his usual environmental position.

The method and technic of giving this drug has changed from time to time as our experience has grown. The dosage has been fixed by Brown at 50 mg. per kilogram weight of patient. The average single amount is 3 gm., the lowest is 1.5 gm., and the highest that has been given in this series is 4 gm. Tryparsamide is given intravenously at about weekly intervals. From five to seven treatments is thought to be sufficient for one series. During the period of treatment, from one to three doses of mercury, intramuscularly, a week is given. At first, tryparsamide was given in successive weekly doses to the amount that has been stated. Recently, the method has been changed, and tryparsamide and arsphenamin have been given in alternate weeks. The reason for this change will be stated later.

Before the patient is given tryparsamide, it is necessary to carry out a careful neurologic study. This is preferably done in the hospital. This examination must include a study of his blood and spinal fluid and a routine examination of his nervous system, together with a general physical examination. In the first series of cases, mental tests were carried out by Dr. Groves B. Smith, particularly in instances in which mental changes were suspected. Recently, this has not been done as a routine. The most important examination outside of that of the blood and fluid is that directed toward the eyegrounds and fields. This work

has been done largely through the aid of Dr. Wiener and his associates, particularly Dr. Alvis, and recently their examinations have been repeated by Dr. Cady or myself in order to accustom ourselves to the slight changes that have escaped our technic. Every patient has been frankly told of the danger of this drug in the matter of vision, and it has been pointed out to each one of them that tryparsamide has a peculiar predilection for the optic nerve, producing defects in vision, in most cases temporary. At the end of the first course or at the beginning of the second course, the patient is admitted to the hospital, where a restudy of his spinal fluid, blood, etc., is made.

Tryparsamide itself seems to be quite inert as far as any general effect on the patient is concerned. In no instance in this series did the patient show any untoward reaction. There was no rise in temperature, no constitutional reaction of any kind and no noticeable discomfort. The immediate after effects are much less positive than in the average run of arsphenamin treatment. The important untoward effect of the drug is the occurrence of amblyopia. In the ninety-seven cases, which include thirteen instances of optic neuritis or optic atrophy, about 27 per cent. showed visual disturbances. This occurs generally after the second dose, but it may occur at any time in the course of the treatment. Usually there is a complaint of dimness of vision, often described as cloudiness or mistiness. The disks examined at this time show no definite changes, but there is a limitation in the field, chiefly a peripheral narrowing. In severe cases, there are scattered and at times central scotomas. Color fields are in like condition. In one or two instances, complete blindness has resulted, but always in cases in which a primary visual or optic disk change was present. In cases, however, of optic atrophy or in the presence of abnormal retinal conditions, the return to the condition before treatment is more difficult to determine, for in such cases if the loss of vision has been progressive before tryparsamide is given, a certain decline of vision is to be expected. In the majority of cases, however, with no previous visual disturbance or defects, no finding of any great importance has resulted and no symptoms have been observed beyond the slight dimness described.

There are in this series, thirty cases of tabes dorsalis, twenty-eight cases of general paralysis or taboparalysis, twenty-six cases of cerebrospinal syphilis and thirteen cases of optic neuritis or atrophy. Under eye symptoms are included all cases in which attention is drawn to vision by any untoward happening or symptom which the patient did not have before treatment. This includes slight blurring, shimmering, shadow, black spots, dimness, and visual defects of all sorts. Thirteen patients with optic atrophy have been treated. Of these, four have now become worse, and nine have shown either slight improvement or their condition is stationary. None of the 30 per cent. other than those with optic

atrophy have shown any visual defects that in any way suggested a permanent change. A fairly definite scheme in regard to method and technic of treatment has been developed. Taking advantage of the spirocheticidal effect of arsphenamin and its derivatives as opposed to the cellular defense of tryparsamide, it seemed logical to give the patient the advantage of both types of therapy in the hope that the activity of the syphilitic process might be met in the two ways here implied. In untreated cases, a series of arsphenamin and mercury as a preliminary stage has been given, after which the patient has been treated alternately with tryparsamide and arsphenamin or the sulphur solution of arsphenamin at such intervals as seems to be established for the individual case. Periods of rest are given when the patient seems to need them. Treatment with mercury is kept up more or less regularly during the whole process of treatment when not contraindicated. In no sense is the treatment a routine procedure.

There have been four deaths in this series of ninety-seven cases, none of which can in any way be attributed to the treatment with tryparsamide. Two deaths resulted from pneumonia; one patient with general paralysis died of a perforated appendix (this was a patient treated at the city sanatorium), and one patient died as a result of a series of paralytic seizures.

In a general and tentative way, the following seems to be a fair conclusion so far as this material is concerned.

If the series is divided into four groups—a taboparalytic group, a tabetic group, a cerebrospinal syphilis group and an optic neuritis or atrophy group—it will be seen that a serologic improvement has been obtained in 93 per cent. of those with paralysis and in practically all others treated. There has been noted a clinical improvement in an average of 85 per cent. of all groups. In those cases in which atrophy or optic neuritis was present, four have grown worse, and nine might be considered stationary. A word might be said as to what is meant by improvement. The serologic improvement does not necessarily mean a permanent change in the cell count or in the colloidal gold curve. In some instances with the cessation of tryparsamide the curve, which had been flattened out, was found to return again to its former state during the period of rest from treatment. In most instances, however, a change once produced in the cell count, Wassermann reaction or curve has remained permanent during the period of observation. Clinical improvement is largely a matter of the patient's statements and observations as to his weight and general appearance. The remarkable conformity of statements on the part of practically all patients that they feel physically much better after the treatment seems a point worth considering. Gain in weight and improved appearance have been found in all the large series of cases so far reported.

Our chief interest has been in the cases diagnosed as general paralysis. Here, as was noted from the early reports, striking improvement was to be anticipated, and a notable change was seen in the manner, speech and behavior of the patients. In two or three instances, this has been extraordinary. A detailed account of improvement is reserved until further observations have been made. In these cases, a more rapid change in the spinal fluid serology has been noted under tryparsamide therapy than has been obtained from any other form of medication. The chief effect has been found in the alteration of the paralytic curve type, the lessening of the number of lymphocytes and the decline in the Wassermann reaction. The same can be said of the blood, although alterations from positive to negative have been more gradual. As a large percentage of persons with tabes do not present a positive blood at the time of treatment, this is of only relative importance.

Tryparsamide has shown no deleterious effect on a patient, and it seems from a constitutional reaction point of view almost an inert substance. The visual defect seen in 30 per cent. of our cases has been practically proved to be temporary. In respect to the cases presenting visual defects due to optic atrophy, not even a tentative conclusion can here be made. In 85 per cent. of our cases, there has been definite clinical improvement. Tabetic patients have shown an almost constant improvement, although in some instances the pain has returned mildly during the interval of rest from treatment. All patients with general paralysis have cleared up mentally to some extent, but this may mean merely an intermission produced rather more quickly than is usually the case. In some cases of optic atrophy, a subjective improvement in vision has been noted, and at least it can be stated positively that on the whole the cases of optic atrophy have shown no important tendency to grow worse. The use of tryparsamide in cases of optic atrophy is therefore not necessarily contraindicated.

The experience so far seems to indicate that tryparsamide in the treatment of neurosyphilis combined with arsphenamin and some of its derivatives and mercury offers for the present at least a more hopeful outlook for these cases than any other drug or combination of drugs that has been tried at the Barnes Hospital. It certainly presents a more advanced type of treatment than intraspinal medication or the use of any other method, and all have been tried out with great persistency in this service.

RESULTS OF ADMINISTRATION OF TRYPARSAMIDE IN SYPHILITIC DISEASE OF THE NERVOUS SYSTEM AND IN CERTAIN OTHER DISEASES OF A NONSYPHILITIC CHARACTER *

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AND

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Tryparsamide is the sodium salt of N-phenyl-glycineamid-p-arsonic-acid. It was first made in 1915 by Jacobs and Heidelberger, and since that date has been extensively experimented with by Brown and Pearce, who have established its biologic actions in normal animals and in animals infected with trypanosomes and with the spirochetes of relapsing fever and of syphilis. Reports from subsequent investigators deal with the use of the drug in the treatment of patients with syphilis of the central nervous system (Pearce, Keidel, Moore and Lorenz, Löwenhart, Bleckwein and Hodges). More recently, a report by Kirby discusses the value of the drug particularly in the treatment of the patient with general paralysis.

In the summer of 1923, in the neurological department of Bellevue Hospital, we used this drug in various types of syphilitic infection of the central nervous system. Our intensive administration of tryparsamide occurred in the summer months, after which we were kindly permitted by the authorities of the Rockefeller Institute to use this remedy in various other diseases of a nonsyphilitic character. The drug was used in doses of 3 gm. (with two exceptions to be specified later), and was given at weekly intervals in series of eight injections. In most instances, two weeks elapsed between the series. The solution contained 1 gm. of the drug to 5 c.c. of sterile, freshly distilled water, and was injected intravenously by the syringe method. Mercury has been used at the same time in the recent stages of treatment in seven of the cases.

Patients with the following types of syphilis have been treated: tabes, thirteen cases; paralysis, seven cases; meningovascular syphilis, nine cases; taboparalysis, one case; mental deficiency with central syphilitic stigmas, one case.

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* From the Neurological Department of the Bellevue Hospital, New York.

* Read at the Fiftieth Annual Meeting of the American Neurological Association, Philadelphia, June, 1924.

TABES

Therapeutic results.—Six patients were improved as regards root pains and four as regards ataxia. Three were not benefited.

Serologic Effects.—Our cases were necessarily ambulant and belonged to a class difficult to control, with the result that in only nine of our patients intensively treated for tabes did we succeed in obtaining satisfactory serologic testing subsequent to treatment. Of these nine, three positive blood Wassermann tests were changed to negative, but only two positive spinal fluids became negative. The colloidal gold curve, significant of parenchymatous change, was reduced quantitatively in four cases and abolished in none. In only three cases did any reduction in pleocytosis occur.

Untoward Effects.—Of ten patients receiving five or more injections, six had no visual complaints; two complained of blurred vision and of flashes of light before the eyes but lacked objective changes, while two had blurred vision and subsequent pallor of the optic disks. Of three patients receiving less than five injections one had no visual disturbances, and two had haziness of vision of uncertain duration without objective alteration of structure.

GENERAL PARALYSIS

Therapeutic Results.—In three patients, no beneficial changes were noted; in two, moderate improvement occurred; and in two, definite improvement occurred. In one of these, the change began after two doses, and led to conspicuous reduction in memory and speech disturbances. Weight and general health improved, and after ten injections, the patient was able to return to work. The benefit in this case was unusual. In the other patient, improvement began after the third dose. Her headaches disappeared, euphoria and confusion decreased, and a speech defect cleared up. There was much improvement in insight and judgment, and the patient was able to resume competent management of her home.

Serologic Effects.—In these seven cases, only one positive blood Wassermann test was reduced—from 4 plus to plus-minus. The spinal fluid Wassermann reaction was reduced in only one instance. The colloidal gold curve was lessened quantitatively in three cases, and abolished in none. Cell counts were considerably changed in five cases; in fact, in all the cases in which the record is complete on this point, the cells were reduced from an average of 20 to 6, 6, 4, 3 and 2.

Untoward Effects.—Of the seven patients, only two had no visual complaints. Four complained of blurred vision without any objective changes, while in one case—that of a patient who had received only

five injections, pallor of the disks appeared, and visual acuity fell to 5/200 in each eye. Our record is incomplete as regards the permanence of these visual changes.

MENINGOVASCULAR SYPHILIS

Therapeutic Results.—Of nine cases, definite benefit was obtained in seven. In four of these, hemiplegic symptoms were greatly relieved. In one case, there was reduction of headache and of root pain. In one, there was diminution in the frequency of convulsions; and in another, paraplegia improved. In two cases, there was no change in the condition.

Serologic Effects.—The blood Wassermann test was changed from plus to negative in only one instance, although partially reduced in two others. The spinal fluid Wassermann test was altered from four plus to negative in only two cases, although reduced partially in two other cases. In the cell count, a large reduction was obtained in two cases; while in four, the pleocytosis remained substantially unchanged or else was slightly lowered. In the five cases in which two or more colloidal gold curves were obtained, the intensity of the reaction was diminished in four.

Untoward Effects.—Four patients had no visual complaints, although of these, two received only two injections. Four experienced subjective diminution in vision in one or both eyes, transitory in nature, without objective changes. In one case, subjective visual complaints arose, described as "fluttering and spots before the eyes." Later, when the series of injections was continued through fourteen, there developed concentric constriction of the fields with lowering of visual acuity to 20/50 and 20/100. After the last injection, there was pallor of the disks and narrowing of the arteries. In this patient, the earlier doses only were full size, and the last seven injections were in greatly reduced dosage—namely, 1 gm. each. Of these cases, one patient suffered a moderately severe rigor after four of the injections. Subsequently, ten more injections were given without that complication, which remained isolated and peculiar to this patient in the entire group.

TABOPARALYSIS

A single patient received nine doses. In this case, there was improvement of a hemiplegia, reduction of confusion, and restlessness and improvement in orientation. There was no alteration of the blood or spinal fluid Wassermann tests; the gold curve remained strongly positive. There was severe amblyopia after the fourth injection, which

lasted several weeks. The nerve heads showed signs of low grade papilledema. Later when an attempt was made to resume injections, amblyopia recurred.

In a case of mental deficiency with central syphilitic stigmas, there were beneficial changes in concentration and memory, together with gain of weight and improvement in general health. Because of the age of the patient, the doses were only 2 gm. each. The blood Wassermann test remained 4 plus, the spinal fluid Wassermann was changed from 4 plus to 3 plus. After eight doses, the count had dropped from 60 to 6, and remained at this level. Also a colloidal gold curve, moderately strong before treatment, had become entirely negative. In this case, there was no visual trouble. The only ill effect was nausea, which followed the seventeenth injection.

MULTIPLE SCLEROSIS

We undertook to treat available cases of multiple scleroosis with tryparsamide, and carried out a relatively short course of injections in three patients. Typical signs of multiple sclerosis in conjunction with the manner of onset and the occurrence of remissions made the diagnosis certain in each case. Because these patients had temporal pallor, we made the dosage only 2 gm. rather than the 3 gm. which we were using in syphilitic cases. We felt that possible beneficial effects warranted cautious use of the drug even in these cases. In two of the patients, who received, respectively, seven and three injections, we noted no change that could be attributed to the tryparsamide. In the third case, on the other hand, a deleterious effect resulted. This patient was given seven injections of 2 gm. each at weekly intervals, and at the end he suffered rather suddenly total flaccid paraplegia with complete sensory loss below the level of the eighth dorsal segment, with incontinence and spinal automatism. The rarity of such a development in multiple sclerosis and its occurrence in association with the tryparsamide treatment gave us considerable pause, and we discontinued the use of tryparsamide in this disease. Gradually, after about eight weeks, this myelitic syndrome disappeared, and the patient fortunately returned to a condition no worse than his initial state. The signs of pyramidal tract involvement reappeared. This patient also suffered severely in visual acuity as a result of the injections, but gradually after a period of approximately four months this too regained its former state. To summarize at this point the question of tryparsamide injections in multiple sclerosis: We consider that brief experience shows that it is contraindicated.

ENCEPHALITIS

The drug was used in 2 gm. doses in six cases of lethargic encephalitis; five patients received eight, and one, sixteen doses. Midbrain and cerebral signs cleared up in the three acute cases, but it is impossible to claim that the drug induced these results, for the changes were not different from those commonly seen in nonfatal cases. However, rather marked tonic benefits in addition were brought about and accord with the ability of tryparsamide to influence nutrition favorably. In none of the acute cases did subsequent pseudoparkinsonian symptoms develop. We can dismiss the question of tryparsamide therapy in encephalitic cases by saying that under certain conditions the tonic effects that can be expected warrant its use in acute cases, if the dose is kept so small as to promise immunity to the optic nerves.

RESULTS IN SYPHILITIC CASES

The risks from the use of tryparsamide are greater than from other forms of treatment because of the frequency of temporary injury to the optic nerves. We are unable conclusively to judge as to the permanence of such injury, although our observations lead us to believe that the optic nerves show a strong tendency to recuperate after the tryparsamide damage and that this repair is assured if in the susceptible cases the drug is withdrawn as soon as the first subjective signs of harm are observed. Such injury is not appreciably dissimilar in the different types of central nervous system syphilis, although, *a priori,* one would expect a greater vulnerability of these nerves in tabetic patients. One patient experienced tinnitus, probably paralleling in the eighth nerve a phenomenon frequent in the second. Other ill effects deemed unimportant ranged from nausea to a chill and occurred in only three patients in the entire series.

We believe that the therapeutic results obtained with tryparsamide compare favorably with the best results obtained with other forms of treatment. This statement applies to all the clinical types of syphilis but more particularly to general paralysis. Tryparsamide exerted a favorable influence on the root pains in a surprisingly large percentage of the tabetic cases. In contrast with these clinical benefits, the serologic results at first glance seem disappointing. An analysis of them, however, shows that the serologic changes encountered relate chiefly to the cell count and to the colloidal gold test, and that these two items show a fairly uniform response under tryparsamide, while the Wassermann reaction in both serum and fluid is more resistant. If we accept the idea that our goal in treating central nervous system syphilis is to alter the reaction of the nervous tissue to the syphilitic infection rather than to free the organism as a whole from the infection, we may assume

Summary of Results in Patients Treated

	Clinically			Blood Wassermann Test				Spinal Fluid						
	Greatly Improved	Improved	Unimproved	Became Negative	Partially Altered	Unchanged	Data Lacking		Became Negative	Remained Negative	Reduced	Unchanged	Increased	Data Lacking
Tabes: Ten patients each received 5 or more injections with an average of 14 injections	4, root pains; 1, ataxia	2, root pains; 2, ataxia	2	3	..	3	4	Wassermann test..	1	1	2	5	..	1
								Cells.....	1	3	2	1	2	1
								Colloidal gold.....	1	..	4	2	1	2
General paralysis: Seven patients each received 5 or more injections, with an average of 12 injections	2	2	3	..	1	4	2	Wassermann test..	..	..	1	4	..	2
								Cells.....	5	..	..	..	..	2
								Colloidal gold.....	..	..	3	1	..	3
Meningovascular syphilis: Seven patients received 5 or more injections, with an average of 16 doses	..	7	..	1	1	2	3	Wassermann test..	2	..	2	1	..	2
								Cells.....	1	1	2	..	..	2
								Colloidal gold.....	1	1	3	..	..	2
Taboparalysis: Nine injections	..	1	..	..	..	1	..	Wassermann test..	..	..	..	1	..	..
								Cells.....	..	..	..	..	..	1
								Colloidal gold.....	..	..	..	1	..	..
Mental deficiency with central nervous system stigmas (24 injections)	..	1	..	..	..	1	..	Wassermann test..	..	..	..	1	..	..
								Cells.....	..	..	1	..	..	..
								Colloidal gold.....	1	..	..	..	..	..

the relatively greater importance of the reduction of pleocytosis and the colloidal curve as a measure of physiologic central nervous tissue adjustment. Tryparsamide therapy, therefore, in the matter of serologic changes, appears to influence most of the tests that have the greater clinical significance.

In general, we believe that the benefits from the drug exceed the untoward effects, since it appears possible and easy to prevent optic nerve changes which are organically permanent, by proper control of dosage. Three grams of the drug is a maximum dose in our opinion, and we believe that it would be better to have 2 gm. established as the average full-sized dose rather than 3 gm. Injections should be given at intervals of at least seven days. It is of practical interest to mention that leakage into the tissues does not cause cellulitis. It is practical to give injections in series of eight consecutive weekly treatments followed by a brief rest period of two weeks. However, there is no definite contraindication to having the second series immediately follow the first. Two or even three series are warranted in cases displaying beneficial results. Improvement, if it occurs at all, almost always occurs early.

Mercury should be used in conjunction with tryparsamide, and we carried out that association in seven of the cases.

Unconditional marketing of tryparsamide seems justifiable if explicit directions regarding dosage and intervals are clearly stated on every bottle and if the dangerous possibilities are sufficiently explained. The drug should not be used on patients when ophthalmoscopic examinations cannot be regularly carried out.

DISCUSSION

DR. HARRY C. SOLOMON, Boston: The whole subject of tryparsamide is of interest. Dr. Schwab's paper especially and Drs. Kennedy and Davis' also have recorded a degree of improvement in patients that seems astounding; certainly Dr. Schwab's report that 87 per cent. of his group of paralytic patients showed serologic improvement and 86 per cent. showed clinical improvement is interesting. The only thing which approaches such results is to be found in other reports on tryparsamide. However, I would like to ask Dr. Schwab for more detail about the serologic improvement, for it will be noted that Dr. Davis reports different serologic improvement from Dr. Schwab.

We have been treating patients who have neurosyphilis for eleven months with tryparsamide, giving forty and more injections. Serologically, our results have been nothing like what has been reported in the literature by the other two men, and what is reported today by Dr. Schwab. We have had cases in which the serology became negative rapidly and cases in which we have not been able to do that with other forms of treatment. We have had cases in which the patients have had almost negative serology with other forms of treatment, and we have put them on tryparsamide with no improvement of the serology. Patients who have improved serologically have, under the continuation of the treatment, reverted serologically and become worse.

In our cases of tabes, we have found little clinical improvement by the use of this treatment. In our patients with general paralysis we have not had a single striking result, therapeutically or clinically.

A patient with general paralysis developed a total amblyopia after four injections of tryparsamide. Nothing was to be seen on ophthalmologic examination; this was checked up by our ophthalmologist as well as myself. This patient died three months after the development of the blindness. The retina, removed at necropsy, showed nothing in the gross to suggest changes, but there was a definite degeneration of the optic nerve. In this case, we should hardly have expected complete improvement.

We have had one other case in which, after a period of months, there was still a marked residual limitation of the visual fields.

Dr. Bernard Sachs, New York: I wish that Dr. Schwab's results and even those of Drs. Kennedy and Davis would be corroborated by all of us.

The reason my experience with this drug has been small is that my medical conscience did not permit me to use the drug or allow my subordinates at the hospital to make wide use of it, because the risk of blindness is so great. I would not consent to the use of the drug unless I were convinced that it was far superior to other methods of treatment.

From Dr. Schwab's remarks and Dr. Solomon's report, I do not think that the evidence is as yet convincing that the drug is superior to other methods of treating syphilitic diseases of the nervous system.

If we can be convinced that the dangers are extremely slight, probably some of us will be less conservative. Many of us are growing conservative with regard to intraspinal injection, and ultimately we shall decide on the safer methods to be used.

Dr. Solomon has reported in his cases that he has seen no great improvement in cases of tabes, and I do not believe that there has been any great clinical improvement in cases of general paralysis. In the case of general paralysis, I should be encouraged to use a dangerous drug if the patient would thereby become a social being able to attend to his business affairs.

Dr. George W. Hall, Chicago: I would like to ask Dr. Schwab how far advanced his cases of general paralysis were. I have had occasion to use this drug in two cases of advanced general paralysis, and both of the patients have grown decidedly and rapidly worse. One of them was easily controlled in his home, before beginning the treatment, but after giving him a series of six doses, he has had to be committed to the asylum because of his great irritability and unreliability; he even becomes dangerous.

The disturbance of vision comes early, as a rule with the first or second dose, rarely later. That disturbance, in the two patients I have treated consisted of the very narrow field of vision; so narrow that in testing them out closely one would think that they were looking through a tube, so to speak. So that, as Dr. Sachs has stated, I have been unwilling to administer this preparation further without having the written consent of relatives or some one who could in some way relieve us from responsibility should any untoward results occur.

Dr. James Ayer, Boston: I should like to summarize the results of tryparsamide therapy in approximately thirty-five patients treated for the most part at the Massachusetts General Hospital, covering the first year of its use by us. The full report is to be found in the paper by Dr. Viets to be read by title at this meeting.

In tabes the results of tryparsamide and mercury therapy were not as good as we have obtained with intravenous arsphenamin or with arsphenaminized serum.

No patient with general paralysis has, in our opinion, been cured, either symptomatically or serologically. On the other hand, we have in a few instances seen marked remissions in cases in which previously other forms of treatment have failed.

We have seen one bad result with regard to the eyes in a patient of Dr. Waterman's who was treated in the same manner as others, i. e., 3 gm. of tryparsamide were given once a week, together with injections of mercury and inunctions. The patient, who had previously had normal vision, after nine injections of tryparsamide developed a well-marked primary optic atrophy. (This patient was seen on July 16. The optic atrophy had progressed to blindness in one eye, with a little better than light perception in the other eye. Mentally, considerable improvement was noted.) Another patient complained of dimness of vision after the sixth injection; contracted visual fields and diminished acuity were present, but both were restored on stopping treatment.

We feel, from our limited experience, that tryparsamide offers little relief in tabes; that in general paralysis it may be of value; but that the danger of optic atrophy from its use is real.

Dr. Sidney I. Schwab, St. Louis: I hope that Dr. Solomon does not believe that I am advocating this treatment with any enthusiasm. I have tried to be conservative. I am not here to advocate tryparsamide as a treatment, but simply to relate an experience in the history of the development of the treatment of neurosyphilis that has taken place in the material at my disposal at the Barnes Hospital. I have not used the word "cure." I certainly did not mean to imply that any patient with general paralysis was cured by this or any other treatment. I referred to certain symptomatic improvements in this group of cases, and a great many of these improvements have nothing to do with general paralysis itself but referred merely to gain in weight, better appearance, increased strength, etc. Then it must not be forgotten that in this series we used arsphenamin and various preparations in addition to tryparsamide and mercury also, so that any improvement may have been due to the continuing of the old method.

In regard to Dr. Sach's kindly attitude toward my venture in speaking about results, I have tried to say how temporary I regard them. These are only notations about what the patients did after having received tryparsamide. At the present time, I am entirely against releasing this drug for general use, because I think it is a preparation that ought to be reserved for hospital use and in cases selected with the greatest care. There are young, ambitious adventurers in St. Louis using tryparsamide in private offices and probably doing great harm.

The patients with general paralysis that we have helped temporarily, fortuitously and accidentally, are patients that could have been treated in the wards of a general hospital. They had no marked dementia and required no particular custodial care.

Dr. Thomas K. Davis, New York: Dr. Schwab's last explanation is probably correct, but I want to add one word regarding the question which Dr. Solomon raised. I think the difference lies in the fact that he used mercury and arsphenamin with the tryparsamide. We did not use arsphenamin in any stage of our treatments and used mercury only in the later stages. Therefore, ours was a tryparsamide treatment.

I would not want to appear to be less conservative than I should be, and I appreciate Dr. Sachs' point of view, but certainly with a disease such as general paralysis, I believe there is danger of being too conservative.

One patient who was treated had been ill for three years; for several months he had been unable to work, and he had severe speech defects and memory defects. He had previously been intensively treated with arsphenamin. We included him in our group of tryparsamide cases, and he immediately became decidedly improved. Last September he returned to his work, involving the handling of figures, and he has shown considerable accuracy in that work and a return of memory function.

THE PATHOLOGY OF THE HEREDITARY AND FAMILIAL NERVOUS AND MENTAL DISEASES *

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The various nervous and mental diseases which show a familial tendency or in which hereditary factors are suspected, are difficult to classify, partly because of group overlapping and partly because the character of the pathologic lesions is often closely comparable in two processes which are quite divergent from the clinical standpoint. An example of the first tendency is the occurrence of cases of hereditary ataxia combining both clinically and anatomically the features of both the Friedreich and the Marie types. An example of the second point may be mentioned in the great similarity of the atrophic process involving the cells of the upper motor neuron in spastic paraplegia and that in the cells of the lower motor neuron in progressive spinal muscular atrophy.

It is obvious that the clinical picture will not be determined by either the nature of the pathologic process or its anatomic locus, but by a combination of these factors and the fact that two widely dissimilar pathologic moments operating on the same locus may give a similar clinical picture (e. g., gumma or brain tumor over the motor area) or that one factor operating on different loci may give widely differing symptoms. Classifications based on the clinical pictures will not serve, therefore, for analysis from the pathologic standpoint.

Separation on the basis of the anatomic locus is equally unfavorable. This will be evident from consideration of Friedreich's and Marie's ataxia and their intermingling.

For these reasons, no concise classification will be offered, but the chief histopathologic features of those conditions which have shown more or less definite lesions will be reviewed in groups showing pathologic or anatomic likeness.

CHRONIC HEREDODEGENERATIONS

A. Progressive Spinal Muscular Atrophy.—The line between the atrophies and the dystrophies was drawn early on the basis of the occurrence in the former of obvious degenerations and losses in the anterior horn cells and their axons. The changes which occur in the

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* Read at the Fourth Annual Meeting of the Association for Research in Nervous and Mental Diseases, New York, December, 1923.

nerve fiber and in the muscle in the spinal atrophies are comparable in all respects to the atrophy which follows experimental nerve section. The typical fatty degeneration of the myelin sheaths with response of phagocytes and fragmentation with gradual phagocytic removal of neuraxon material shows no noteworthy difference from a section-atrophy of the nerve, and the muscle undergoes a progressive shrinking of individual fibers, with moderate relative, but probably little actual, increase in interfibrillar connective tissue and with little or no increase in sarcolemma nuclei; again in close parallel to the results which follow severing of a motor nerve. In sharp contrast to this, is the picture in the dystrophies in which marked muscle fiber wasting with connective tissue increase and striking multiplication of sarcolemma nuclei are found, with no demonstrable nerve cell or fiber alteration. That nerve cells which appear entirely normal by the comparatively coarse measure of even our best histopathologic procedures may still be distinctly abnormal, may be said to be not only possible but highly probable. I have carried out a considerable series of experiments with this in mind and have data on definite indications of a nervous death which leaves behind little or no trace of *structural* nerve cell change. Such a procedure is the acute fatal intoxication by intravenous injection of oxalic acid in the rabbit. Such animals die in convulsions in an astonishingly short time but show by the ordinary histologic methods no consistent nerve cell lesions.

In the central atrophies, the changes in the nerve cells are generally described as sclerotic. Further description of this condition will be given later.

B. Hereditary Ataxias.—This group (including both Friedreich's and Marie's form and mixed cases) seems to show much the same type of chronic atrophic nerve cell process as the preceding, but in addition usually a coarse glia fibril felt work, often vacuolated, which is somewhat out of harmony with the type of simple columnar replacement which has come to be associated with destructive columnar lesions in the cord. The scar in secondary pyramidal tract sclerosis, in tabes and in multiple sclerosis is a replacement by fine glia fibrils deposited in an orderly columnar arrangement following closely the architecture of the atrophic tissue which they have replaced; rarely are the fibrils coarse or felted. In the hereditary ataxias, however, this reaction is emphasized. We have come to look on such scars in other pathologic processes within the brain as differently determined than the orderly replacements. For example, where there is partial occlusion of a vascular stem by endarteritis, orderly scars conforming to the original architectural plan of the cortex, cerebellum or cord are usually the result, but where the occlusion is complete and especially where such occlusion

is sudden, there results, as a rule, a tangled, coarse, fibrous scar. The size of the area apparently plays little part except that when large the center undergoes liquefaction, but at the margin the glia reaction is still that of felt work. Pyramidal tract degeneration secondary to capsular hemorrhage gives a characteristic fine fibrillar columnar scar (though often not so typical as in tabes), and this would seem to indicate that the simple autolysis and resorption of nerve fibers and their sheaths even though their death be simultaneous (i. e., not progressive as in tabes) is not sufficient to cause a tangled mat reaction. In columnar gliosis, we would hypothecate a stimulant action toward proliferation of glia cells by some of the products of autolysis of sheaths or fibers. These factors we would also expect to be operative in the progressive death of fibers in the hereditary ataxias, and the presence of the coarse matted glia scar may indicate some additional factor. It is interesting to note in this connection that in combined system disease associated with pernicious anemia vacuolization and irregular glial replacement is much more common than columnar gliosis, and that a familial origin has been suggested in these cases by Jendrassik.[1]

Another rather striking element in reports is the constant record of marked changes in the vessels, and from this some writers have been led to assume a low grade infective or inflammatory process. Again, in the somatic tissues, there seems to be evidence that similar autolytic products may stimulate the proliferation of mesodermal connective tissue cells. Alzheimer[2] has pointed out the freedom with which quantities of degeneration products are transported from within the nervous tissues to the vessels for ultimate resorption and evacuation. We have no direct evidence, however, of what part products of degeneration of the ectodermal derivatives in the nervous system (nerve and glia cells) may play in stimulating proliferation of the mesodermal tissues (vascular elements). For the most part, the ectodermal and mesodermal tissues within the brain have rather distinctive reactions. In most exudative conditions, as, for example, the leukocytic infiltrations of acute infections or the lymphocytic and plasma cell exudates in paresis or cerebral syphilis, the infiltrating mesodermal cells tend to invade only the mesodermal tissues of the vessels and meninges and strikingly respect the border between mesodermal and ectodermal derivatives formed by the membrana limitans. It is, however, conceivable that certain types of degeneration products derived from brain tissue might cause reaction on the part of the mesodermal cells of the vessel walls and that this might account for the vascular reactions found in

1. Jendrassik, E., in Lewandowsky: Handbuch der Neurologie **2,** Pt. 1, 1912.
2. Nissl and Alzheimer: Histol. und Histopath. Arbeiten **3,** Pt. 3, 1910.

the ataxias and certain other degenerative nervous diseases, notably Huntington's chorea and syringomyelia. It would seem that this question might be approached by direct experiment, by the injection of autolytic products of the brain into mesodermal tissues.

C. Familial Spastic Paraplegia.—Two types of alterations have been described in this group: (1) a cellifugal degeneration dependent on a primary sclerotic change in the Betz cells with secondary axis cylinder death and (2) a cellipetal atrophy beginning in the distal extremities of the fibers of longest course (i. e., lumbar cord pyramidal fibers) and gradually progressing toward the cell body. In neither are the ultimate cell and fiber pictures or the resultant scar reactions strikingly different from the changes in spinal muscular atrophy. Marinesco considers the process to be basically the same in both cellifugal and cellipetal cases.

D. Hereditary Optic Atrophy.—The lesions described seem to be characterized by simple chronic degenerative processes primarily of the nerve cell bodies or their axons leading to the picture of cell sclerosis.

All of the preceding clinical conditions (progressive spinal muscular atrophy, the hereditary ataxias, familial spastic paraplegia and hereditary optic atrophy, together with thirty or more clinical intermixtures) have been grouped by Jendrassik and others into one family, the "chronic heredodegenerations," largely on clinical grounds, and it is interesting to note that from the histologic standpoint the changes are sufficiently similar to warrant a similar grouping. Such differences as are recorded are chiefly in the reactive glia scars and the mesodermal tissues. The basic nerve cell changes here have attracted the interest of a number of observers. The typical sclerotic cell, when the condition is advanced, has been reduced by lateral shrinkage from a rounded or pear-shaped body to a narrow angular pyramid with a narrowed, elongated, elliptical or angular nucleus and with a marked tendency toward deep staining with the basic dyes which are used for the demonstration of the protein fraction of the cell cytoplasm. The apical process also partakes of this pyknosis and is therefore usually easy to trace for a considerable distance from the cell body and often exhibits a rather distinctive wavy contour. In advanced stages the pyknosis of the cell body is so great that no details of the cytoplasm can be made out and the outlines of the nucleus may be obscured, even in well differentiated preparations.

Nissl,[3] in describing this condition, which he called "chronic cell alteration," outlined the initial steps as follows. First, there is loss of tigroid bodies with vacuolization associated with fatty droplet inclusions giving a marbled appearance to the cytoplasm which does not extend

3. Nissl, F.: Neurol. Zentralbl., 1896.

far into the processes. From this stage, the nucleus becomes angular and pyknotic and the cell assumes the characters described above.

Marinesco [4] compares the first steps with the early phases of axonal reaction. He holds that the intracellular fermentative activity may be modified by mechanical, toxic or infectious injury and that under these conditions the proteolytic ferments within the cell break down the tigroid material by hydrolysis, thus accounting for the disappearance of the tigroid bodies and that this autolytic hydrolysis results in an increased number of molecules. As the osmotic tension is in proportion to the number of molecules, it also is increased, water is imbibed and the cell swells. The cell membrane is, however, damaged by the autolytic cleavage and the imbibed water and split products diffuse, and as a result of this the cell shrinks. Marinesco offers as a parallel to this condition the progressive dehydration of the cell with reduction in its volume characteristic of senility.

Schaffer,[5] in discussing the cell changes common to the whole group of the heredodegenerations, agrees with Nissl that the initial step is reduction in tigroid material, but disagrees with Nissl's view that the vacuoles are the result of lipoid droplets. Schaffer considers them to be a result of destruction of the tigroid substance. At this stage, swelling occurs (Marinesco [4]) and then shrinkage begins. Schaffer adds, however, a description of the intracellular neurofibril reaction. At first, the fibrillar picture appears coarsened by cohesion of finer fibrils, and they stain with a massive incrustation with silver stains. Soon, however, they break up, first, into cylindrical fragments, then into smaller blocks and finally into dustlike particles. During this fragmentation they do not undergo fatty degeneration, but continue to exhibit the characteristic argentophilic reaction, thus producing Schaffer's silver granule (silberkörnige) degeneration.

LENTICULAR DEGENERATIONS

There has been a progressive tendency to bring into a related group a wide variety of clinical pictures characterized pathologically by cellular degenerations in the lenticular nuclei and clinically by dyskinesia. Within this group are to be found the chronic choreas, progressive lenticular degeneration, pseudosclerosis, bilateral athetosis, etc. The last three show a characteristic hepatic cirrhosis and thus constitute a separate subgroup often listed as hepatolenticular degenerations. That this is not a pure group is shown by the occurrence of cases without cirrhosis.[6]

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4. Marinesco, G.: Rev. neurol. **29**:166, 1922.

5. Schaffer, K.: Schweitz. Arch. f. Neurol. u. Psychiat. **7**:200, 1920.

6. Wimmer: Rev. neurol. **28**:1206, 1921. Alzheimer, A.: Ztschr. f. d. ges. Neurol. u. Psychiat. **33**:45, 1916.

Cécile and Oskar Vogt[7] have classified the pathologic processes in the striate body as follows:

1. Marbled (étât marbré), which is characterized in the gross by a mottled appearance of the striate and some reduction in volume but without gross cavitation. Microscopically there is marked loss of cells, moderate glia fibrillar replacement and heterotopic bundles of myelinated fibers. Double athetosis is the clinical parallel of this.

2. Fibrous (étât fibreux), which is characterized by elective necrosis of the ganglion cells and finer nerve fibers with crowding together of the remaining coarse fibers and marked glia scarring. This is found in chronic bilateral chorea without dementia and with added cortex changes also in Huntington's chorea.

3. Necrosis, which is marked by the alteration of the striate body to a spongy, porous mass through destruction and resorption of the ganglion cells and their processes, with little or no glial replacement.

4. Hemorrhages and softenings. These need no description.

In cases of Wilson's disease, the necrosis is readily visible to the naked eye, there is little reactive change on the part of either the plasmatic or fibrous glia, and the cortex is usually not involved. In pseudosclerosis and double athetosis, however, the gross changes are less marked. Often little can be observed by the naked eye, although frequently a striate body with comparatively normal appearance will be found to be distinctly less resistant to palpation than the surrounding tissues. Often there is some visible reduction in volume and in the fresh brain a mottling of the surface with pinkish or faint purplish irregular patches. After fixation in formaldehyd, the affected area is frequently more easily seen and at times takes on a distinct yellowish cast. In one of the writer's cases no visible alteration could be made out in the fresh brain, but palpation revealed a distinct loss in resilience and after fixation the marbled appearance was readily seen. Microscopically, these ganglia show a striking loss which is almost selective for the larger ganglion cells and their processes and in addition a much greater glia reaction than in Wilson's disease. This is in part made up of true fiber-producing cells and their fibers, but there are present also many large multinucleated cells of the ameboid type with large amounts of cytoplasm (giant glia cells of Alzheimer) which are not fiber formers, and many bizarre nuclei with little or no cytoplasm. The latter are often extremely large, vesicular with small granules of chromatin lying at the nuclear membrane and an extremely translucent

7. Vogt, C. and O.: J. f. Psychol. u. Neurol. **24,** No. 1 and 2, 1918

body. Their form is occasionally a regular oval, but much more commonly they are strikingly irregular. Many show constricted or indented bodies and often large lateral budlike extensions, so that repeated change of focus of the microscope is required to follow their outlines in various planes. Alzheimer [8] and Bielschowsky [9] have both called attention to the similarity of the giant glia cells to forms seen in tuberous sclerosis and consider them evidence of developmental anomaly. Bielschowsky lists the characteristics of the three processes as follows: total necrosis without scarring in Wilson's disease, fibrous gliosis in chorea and this embryologic moment in pseudosclerosis. The bizarre nuclear forms are more frequent in the gray matter, but are reported also by Hall [10] in the white matter, and I have seen them there in numbers in one of my cases. They are not limited to the striate body, but similar forms although often less striking are to be found in wide distribution through the cortex, cerebellum, medulla, etc. From the histologic standpoint, those cases of bilateral athetosis in which careful examinations are recorded seem to be practically identical with the pseudosclerosis group. Pseudosclerosis is in contrast with Wilson's disease from the clinical standpoint by the development of a progressive dementia, and parallel to this the histologic reports show variable degrees of involvement of the cortex, both in cell degenerations and in the occurrences of the characteristic glia cells. Alzheimer's [6] last paper—published after his death—was a report of a case of bilateral lenticular degeneration associated with posterolateral sclerosis and with many lesions in the cortex.

There is a large series of studies on record, both at home and abroad, on Huntington's chorea, which agree closely in the main essentials. The predominant attack here is on the small cells of the putamen and nucleus caudatus with a constant fibrous gliosis, which may be only a replacement, or more characteristically is an active intense scar formation with large astrocytes and coarse fibers. The cortex is also consistently involved, with a fairly diffuse distribution of the lesions but with a rather striking tendency to avoid the occipital and temporal poles. The precentral, postcentral, frontal and prefrontal zones bear the brunt of the attack, which also shows a tendency to select certain laminae in these fields. The greatest losses are usually in the external granular layer (Lam II) the pyramidal layer (Lam III) and the internal granular of stellate layer (Lam IV). The ganglionic layer (Lam V) is usually less affected than others, and this is notably true of the larger

8. Alzheimer and Hoesslin: Ztschr. f. d. ges. Neurol. u. Psychiat. **8**:183, 1911.

9. Bielschowsky and Freund: J. f. Psychol. u. Neurol. **24**:20, 1918.

10. Hall, H. C., quoted by Hadfield, Geoffrey: Brain **46**:147 (July) 1923.

cells of this layer, e. g., the Betz cells of the motor cortex. Winkelman and Wilson,[11] in their report of a case, note an apparent exception to this. They state that "only an occasional Betz cell remained." In another place, however, they state that the internal capsule showed no degeneration and the cord showed no degeneration, so it seems probable that they misinterpreted the normal gaps between the nuclear clusters of Betz cells as areas from which there had been losses. The early stages of the cell alterations in the striate body are difficult to determine because of the practically complete devastation here before the case comes to necropsy. In two of Alzheimer's cases, he reports finding no cells capable of functioning in the ganglia. Such changes as have been observed (chiefly in the cortex) are characteristic chronic cell alterations but differ radically from those of the heredodegenerations described above in that there is a heavy load of lipide degeneration products here. Moreover, as the cells undergo chromatolysis and begin to disintegrate, there is also a strong neuronophagic reaction which is lacking in the other group. As would be expected, the fuchsinophil granules which Alzheimer [2] considered as precursors (Vorstufen) of lipides [12] are present in quantities in many cells which have not yet been severely affected. Alzheimer also lays special stress on the number and character of the ameboid glia cells which are found in chorea. He feels that here they live much longer than their usual fleeting period and remain to become a permanent part of the scar.

Kolpin [13] has studied the cyto-architectonics of a choreic brain and records retention of stellate cells (Lam IV) in the precentral field, an unusually broad granularis profunda (Lam IV *c*) in the area striata and an overrich granularis interna (Lam III) in the visuopsychic area. He interprets these anomalies as evidence of an infantile or juvenile type and infers a developmental background on which the degenerative lesion develops.

One other group of changes separates Huntington's chorea from most of the other hereditary degenerations. This is the striking proliferative and degenerative response of the white fibrous connective tissue. Pacchymeningitis and leptomeningitis with marked vascular fibrosis and hyaline degeneration of the newly formed collagen fibrils form a striking element in practically all descriptions. This has led to the suggestion of a chronic inflammatory factor operating on defective soil in Huntington's chorea, but again we are faced with a lack of infor-

11. Winkelman, N. W., and Wilson, G.: Acute and Chronic Chorea, Arch. Neurol. & Psychiat. **9**:170 (Feb.) 1923.

12. This word is used instead of lipoides in accord with recent nomenclature of biological chemistry.

13. Kolpin: J. f. Neurol. u. Psychol. **12**:57, 1908.

mation concerning the capacity of the by-products of brain disintegration to stimulate connective tissue overgrowth in the absence of other inflammatory agents. The great loss of brain cells by a process which includes active fatty degeneration of their cytoplasm might conceivably yield in a chronic process sufficient stimulus for such a reaction. It is also interesting to note that here also, as in the hereditary ataxias, in which vascular thickening occurs, the gliosis is intense and coarse fibered.

AMAUROTIC FAMILY IDIOCY

This disease process is of great interest, first, because it is an instance of an acquired mental deterioration (i. e., dementia) with onset at a very early age (the clinical history in practically every case lays stress on the normal or bright early months in these cases, so the term idiot is misused); and second, because of the extreme spread and intense character of the nerve cell degenerations. Much interest attaches to the possible occurrence of dementing processes in early life as an explanation of many cases which have been interpreted as mental defect, but in which the family history of defect so common in many types of defectives is not convincing. Histologic studies show that no other pathologic process, except possibly simple chromatolysis, exhibits such a widespread and unselected attack on all nerve cells. Schaffer says that it involves every nerve cell from the frontal cortex to the conus gray, and this widespread process also results in astonishing morbid pictures with complete disappearance of the Nissl bodies and marked swelling of the cells with an enormous load of débris.

One of the best descriptions is that of Alzheimer[2] taken from a case of the Tay-Sachs type.

> There are massive collections of granules of specific types in both ganglion cells and glia cells. The cell bodies are swollen by the accumulations. There is a change in form like that which occurs in fatty degeneration but much more pronounced. Pyriform swelling of cell bodies occurs, as well as sack-like protuberances of lateral processes and balloon or spindle formed dilations of apical processes. In preparations stained by the Nissl or Bielschowsky methods a fine fibrillar network of cytoplasm or fibrils supports the degeneration products. The same substances are to be found in the glia cells and deposited in the adventitial spaces.

At first, these included materials were considered to be like the lipides of senile degeneration, but the scharlach R reaction is a striking variable in different cases, and the stainable substances are not comparable in extent to the deposits. They also fail to blacken consistently with osmic acid after chrome fixation. They can be stained, however, by several methods and almost electively so by the Weigert myelin sheath method. They are soluble in hot alcohol and in ether, and there-

fore are to be classed as lipides. They stain a light blue with May-Grünwald stain and in Ehrlich's hematoxylon after formaldehyd fixation. The differential staining reactions between these accumulations and the lipides of senile dementia are as shown here.

Amaurotic	Method	Senile
Slight or none	Scharlach R	+
+	Weigert	±
+	May-Grünwald	—
+	Ehrlich	—

The glia response is chiefly phagocytic though in part reactive. The phagocytes contain lipides which give as a rule a stronger sharlach R reaction than the intraneuronic deposits, while those in the adventitial spaces stain strongly, thus suggesting a gradual reduction to the simple fatty degeneration products during transportation to the vessels.

Degenerations of fibers and sheaths in the white matter are rare, although there is often a distinct delay in the maturation of certain myelogenous zones.

The intracellular fibers here as in many other degenerations (e. g., Alzheimer's disease and the chronic silver granule degeneration described above) seem very resistant to disintegration, and swollen fibers can be stained after the other cellular changes are advanced. The axis cylinder process is rarely involved (Schaffer), and the extracellular fibrils are usually intact.

From the standpoint of histopathology, most workers agree that the two forms, the Tay-Sachs (infantile) and the Spielmeyer-Vogt (juvenile) in spite of some rather distinctive clinical differences must be considered as merely different expressions of the same disease modified by the stage of maturity of the nerve cells and by the severity of the process (Alzheimer, Schaffer, Walter). Walter [14] cites cases falling between these two groups both clinically and pathologically and notes that the dementia is variable and that some forms show only slight mental enfeeblement. Stargardt [15] emphasizes the fact that in cases of familial progressive macular degeneration, which is characterized by progressive degeneration of the rods and cones in the macular region, there is a wide range of mental change and that many patients show no demonstrable dementia. He believes that careful examinations, with a mydriatic, in all those with defective minds and those with dementia would reveal many such cases.

Walter discusses at some length the reports dealing with various developmental defects and coincidental inflammatory lesions of the brain, and concludes that these anomalies and gross lesions form no essential part of the process.

14. Walter, F. K.: Ztschr. f. d. ges. Neurol. u. Psychiat. **40**:349, 1918.
15. Stargardt: Arch. f. Psychiat. **58**:852, 1918.

Schaffer [16] reports a number of cyto-architectonic variants which he feels are important. First the granule layer (IV) overlaps in the precentral field which is seen in some monkey brains; second, the area striata extends onto the lateral surface of the hemisphere to a considerable degree, again as in the ape's brain; third, the area striata in places has ten layers, as is seen in the cortex of the capuchin monkey (Brodmann). On the basis of these three pitchecoid features, Schaffer hypothecates a primitive or defective cortex, a micromorphologic stigma of degeneration in the sense of Pick and therefore a neuropathologic disposition which forms fertile soil for the implantation of the disease process. It seems to me that Schaffer falls into the uncritical anthropomorphic error of considering man's brain to be of the highest possible development and any deviation therefrom to indicate a regression. Such a thesis would certainly be difficult to establish in the case of the olfactory cortex, for example, and experiments seem to indicate that certain insects, notably the bee, can receive visual stimuli in the ultraviolet.

Schaffer believes that the great load of lipides in the cytoplasm is the result of rapid breaking down of the hyaloplasm and a massive accumulation of the degeneration products so derived. Alzheimer concludes that at present it is impossible to decide between a defect in synthesis and a degenerative process. The tigroid masses are practically entirely absent in cells in the advanced stages, and Mott [17] has shown that this striking loss is paralleled by a great loss in nucleoprotein content of the nervous system as a whole, and he considers the process as a constitutional disease of metabolism of the ganglion cells. The tigroid bodies because of their staining reactions are looked on as an extranuclear nucleoprotein. The nucleoproteins are loose combinations of nucleic acid and proteins. Nucleic acids from animal tissues contain phosphorus, the source of which according to Miescher [18] is in the phospholipides. Three possibilities present themselves here: First, failure of synthesis of nucleic acid leaving the phospholipides as an unused store of raw material within the cell body; second, rapid consumption of the nucleic acid permitting the phosphorus-free fraction to accumulate in the cells and, third, a lowered rate of hydrolysis or excretion of the phosphorus-free fraction by the cell again permitting an accumulation. It would seem that the first and third hypotheses were more in harmony with the age and stage of development of these cases than an excessive catabolic activity such as is envisaged in the second.

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16. Schaffer, K.: Ztschr. f. d. ges. Neurol. u. Psychiat. **46**:1, 1919.
17. Mott, F. W.: Arch. Neurol., London, 1907.
18. Miescher, F., quoted by Robertson: The Chemical Basis of Growth and Senescence, Philadelphia, J. B. Lippincott Company, 1923.

EPILEPSY

In considering epilepsy among the hereditary or familial diseases, it is essential that the line be clearly drawn between the "common" or idiopathic form of the disease and symptomatic epileptiform conditions associated with many focal brain diseases. Alzeimer, after excluding cortical epilepsies, assigns the remainder to four groups:

1. Those associated with certain developmental defects of the brain.

2. Those developing from various encephalitides that give the picture of epilepsy and idiocy—especially focal meningeal and vascular lesions.

3. Those resulting from general diseases, such as syphilis, arteriosclerosis, intoxications with alcohol, with lead, etc.

4. Those including an etiologically unclear group of cortex diseases which lead to atrophic scleroses of the brain.

Groups 2 and 3 are obvious acquired diseases and do not interest us here. Group 1 probably is better considered with the general topic of brain defects. Group 4, however, contains the majority of the so-called idiopathic epilepsies in which familial occurrence is common. Approximately 60 per cent. of these show varying degrees of sclerosis of Ammon's horn, which was first described by Worcester in material from the Danvers State Hospital, Mass. Striking gliosis of the zonal layer of the cortex (Randgliose) is also a frequent finding. Alzheimer holds that both of these are reactions of the glia to losses of nerve cells and fibers which form the basis of the epileptic dementia. These changes, especially the zonal gliosis, are marked in advanced dementia and slight in the earlier cases, comparable to similar change in the paretic brain. Acute changes in the ganglion cells occur, particulary in status epilepticus. These changes in the ganglion cells are not especially striking, but they cause a great reaction on the part of the glia cells resulting in the production of great numbers of ameboid glia cell forms with a variety of cytoplastic inclusions. But neither the ganglion cell changes nor the ameboid cell reaction is characteristic of epilepsy.

HYPOPHRENIA AND DEFECTS

Again, the nature of our selection requires the rigid exclusion of brain defects which are caused by accident or disease, in either the intra-uterine period or in early childhood. There is, however, a very large group in which genetic studies have established fairly clearly, if not an hereditary, at least a strong familial incidence. These may be conveniently divided into two groups: First, those with distinctive gross brain defects and, second, those with brains which by gross inspection would appear to fall within normal limits as to both size and convolutional pattern. The first forms an extremely heterogeneous group,

exhibiting a great variety of developmental defects. Perhaps the most interesting condition in this group is microcephalia vera in the sense of Giacomini, which is that of a high grade but seemingly equal lack of development in all parts of the brain. These cases are not infrequently familial. Vogt [19] records five cases in one family. He considers them as probably an endogenous primary aplasia, and notes that siblings have a strikingly similar brain weight. In typical cases, the cortex pictures conform fairly accurately to the stage of development of the cells at the period of maturity at which development ceased. Thus both Hilty [20] and Tramer,[21] who studied by different methods the brain of the 49 year old microcephalic Cecilie Gravelli under von Monakow, concluded that her brain (which weighed at death 370 gm.) represented the result of a check in development operating at about the fifth to sixth month of intra-uterine life and conformed with considerable accuracy to the normal development at that period.

Giacomini considered that pseudomicrocephalia, i. e., in those cases in which there were unequal checks on development in different parts of the brain, was usually the result of fetal brain disease. Apparently, however, this rule cannot be applied too rigidly. Even in microcephalia vera the lower brain parts—cerebellum, pons, medulla, basal ganglia, etc.—are usually approximately normal in size and development, and if the cortex of persons with microcephalus is studied from the architectonic standpoint, various anomalies, such as heterotopic cortex in the white matter and abnormalities in size and form of nerve cells, are found to exist, as well as simple unfinished cortical structures.

Cases of mental defect with "normal-looking" brains form a group of entrancing interest to the neuropathologist. Naturally, such brains are to be found in greater proportion in the lesser grades of defect.

In Willmarth's [22] series of 100 brains of feebleminded children reported from Elwyn, Pa., he lists twenty-five as showing no actual disease or imperfect development of the brain and an additional six showing no actual disease or involved development of the brain but hypertrophy of the skull, so that at least 25 per cent. and possibly 31 per cent. of his cases must be looked on as falling within the normal appearing group.

That brain weight will not serve as a criterion of functional capacity is well recognized by those who have been at work in this field and is nicely exemplified in the Waverly Research Series—Cases 1 to 10 by

19. Vogt, H., in Lewandowsky: Handbuch der Neurologie **3,** Pt. 2, 1912.
20. Hilty, O.: Arbeiten aus, d. Hirnanat. Inst. in Zurich **2,** 1905.
21. Tramer, M.: Arbeiten aus d. Hirnanat. Inst. in Zurich **10,** 1916.
22. Quoted by Southard: Mém. Am. Acad. of Sc. **13**:2, 1918.

Fernald, Southard and Taft.[22] In that study, Case 5, in which the patient was subnormal; Case 10, in which the patient had a mental age of 2.4 years, Binet test; Case 9, in which the patient's mental age was 7 according to the Binet test, and Case 4, that of a moron or subnormal person, all exceed both the normal average brain weight for their age and sex and also the calculated brain weight according to Tigge's formula; while Case 8, that of a subnormal, executed murderer, comes close to both figures.

Hammarberg and Tredgold both believed that feeblemindedness was explainable on actual numerical deficiencies in nerve cells in the cortex. Mierzejewski[23] feels, on the other hand, that often there are a sufficient number of cells, but their interconnections are improperly developed, and he quotes Déjerine as likewise believing that intellectual capacity probably depends more on the multiplicity and extent of intercommunications than on the number of cells.

That measurements of the depth of cortex will not prove a safe guide seems obvious when we consider that in addition to the essential nervous elements here (cell bodies, dendritic and lateral process extensions, terminal arborizations of afferent fibers and propriocortical axons) we probably have a strikingly variable amount of supportive tissue. This is particularly difficult to estimate by direct observation in the gray matter, where there is apparently a lesser complement of fibrous glia and a considerable quantity of material of glia origin which is not differentiated into fibers.

That counts of the cells in given cortical areas will likewise fail seems indicated by the fact that unless cognizance is also taken of their spacing, no estimate can be made of the relative richness of their interconnections.

In reviewing this subject some years ago,[24] I suggested the use of a threefold coefficient of correlation between cortex depth, cell size and cell numbers as a promising approach to this problem, and further work along this line, in an animal experiment, is now under way.

Factors which may operate to prevent full brain development and which might conceivably be determined by hereditary or familial limitations may be outlined as follows:

1. Quantitative failures. This is the factor to which Southard assigns the term plastic impotence or agenesis and would operate by a lessened capacity of the germinal epithelium to produce primitive neuroblasts. This would produce a brain with a deficient number of cortical cells, but such cells might be well developed and capable of normal function.

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23. Mierzejewski: J. Ment. Sc. **24**:562, 1879.
24. Orton, S. T.: J. Nerv. & Ment. Dis. **47**:5, 1918.

2. Qualitative failures. In this would be included probably both agenesis as above and also aplasias (plastic arrest). Several possibilities enter here, most prominent of which would be the following.

(*a*) Arrest of migration. Many cortical pictures give evidence of failure of normal complete migration of the primitive neuroblasts from the site of their origin around the neural canal to their ultimate goal in the cerebral cortex. Such arrests would explain the heterotoptic inclusion of ganglion cell clusters in the white matter as well as the frequent finding of cells of the fusiform layer (VI) scattered irregularly in the white matter below the lower cortex limits. Often, it is difficult to determine with any accuracy the exact bottom limits of the cortex because of the occurrence of scattered cells of this type. I [24] estimated the error of cortex depth measurement entering in this way at about 3 per cent.

(*b*) Arrest of differentiation or maturation of individual cells. That this factor is operative in cases of idiocy, is shown by Hammarberg's [25] work. His illustrations show excellent examples of immature nerve cells in all levels of the cortex, and, while generally also associated with marked quantitative lack, various phases can be seen from a general lack of mature differentiation in all cells, to those in which some cells are well differentiated and others quite immature.

It is possible that this factor may also play a part in abnormal lamination patterns. In discussing the loss of the stellate layer (Lam IV), in the precentral cortex, Brodmann [26] says no statement can be made as to whether these cells, which are present early, are later destroyed or are scattered into neighboring laminae. The relatively greater thickness of the overlying layer of pyramidal cells (III) and of the subjacent ganglionic layer (V) when contrasted with the nearest cortical field (the postcentral) would seem to indicate the possibility that the fate of the primitive cells of this layer is neither to regress (Zurückbilden) or to be scattered (Zerstreuen) as Brodmann suggests, but rather to undergo a selective differentiation into stellate cells or granules of layer IV in the postcentral field and into pyramidals of layers III or V in the precentral field.

In all of the foregoing groups, one must recognize the hypothesis that limitations either by heredity or by unfavorable conditions for growth and development either in the intra-uterine or infantile period may operate *selectively* on the neuroblasts without interfering with the growth of the supportive tissues. Observations in acquired degenerations—especially the ischemias of endarteritis—seem to indicate that

25. Hammarberg, C.: Stud. u. Klin. u. Path. d. Idiote, Upsala, 1895.
26. Brodmann, K.: Vergleichende localizationslehre, Leipzig, 1909.

the glia may survive and proliferate under conditions which lead to complete destruction of the nerve elements. If a similar differential check be supposed to be operative during development, a comparatively normal growth of the supportive materials might be concurrent with a decided check in neuron development. The result of this might easily be a brain of good size (i. e., within the "normal looking" group) but with a decided defect in nerve cell equipment. Hammarberg states that some of his cases led him to the conclusion that there was a disproportionately large amount of supportive material, and, if we may assume that the richness of interconnections between cells in the cortex is in relation to the stage of morphologic maturity of the cells, some of his illustrations would seem to demonstrate this.

COMMENT

In the series of disease entities and groups here discussed, three main pathologic moments may be recognized which from their familial occurrence seem to be determined by heredity or by similar congenital factors. These three moments are an agenetic, a paragenetic and a catagenetic.

1. The agenetic is well explained by Southard's term plastic impotence and is characterized by defective quantitative development. Its expression is seen to best advantage in microcephalia vera, and it also probably forms the background of many cases of milder mental defect. That it may also be operative in other processes, is shown by the frequent report of agenetic findings in association with other types of hereditary or familial diseases. Many authors (Marie and Senator, Bing, Barker et al.) record the finding of small cords or cerebella in the hereditary ataxias which they consider evidence of a development defect. Alzheimer questions this on the ground that it may be the result of fiber and medullary sheath losses without compensatory glial replacement. Jansky reported one case and Bielschowsky three cases of cerebellar aplasia in amaurotic family idiocy.

2. The paragenetic moment is characterized by qualitative structural differences in the nerve or glia cells or in positional misplacements of elements. Alzheimer and Bielschowsky both hold that the characteristic giant glia cells of pseudosclerosis are of such an embryonic origin. The occurrence of a granule layer in the precentral cortex in an amaurotic idiot as recorded by Schaffer and in chorea by Kolpin would be interpreted as of this nature. There is here no lack of numerical development but a failure in ultimate differentiation or distribution. One of the best illustrations of this type of change comes from a disease which is considered to be neither hereditary nor familial, but which exhibits

paragenetic phenomena in both nerve cells and glia to excellent advantage. This is tuberous sclerosis, in which bizarre giant ganglion cells and unusual neuroglia cells form, and heterotopias occur.

3. The catagenetic group consists of cases in which a defective development results in a nervous system which either as a whole or in certain of its parts is subject to striking recessive or degenerative changes. The agenetic and paragenetic include for the most part those conditions which are readily recognized as inherent defects, chiefly the various degrees of mental enfeeblement and central nervous system aplasias. The catagenetic, on the other hand, includes that group of cases with comparatively normal function for a greater or lesser period and presumably therefore a structure which is within the normal factor of safety for the nervous system but in which there later occurs a selective degeneration whose hereditary or familial incidence indicates an intrinsic weakness.

The neuron must be considered not only as a structural unit of the nervous system, but also as a unicellular individual living in so close a symbiotic relationship with other cells that even life is impossible to it if separated from them. In spite, however, of the extreme interdependence of this symbiosis, the cell is still an individual which must carry on its own metabolic interchange with the surrounding body fluids and which may suffer regressive changes to a greater degree than its neighbors in the community.

There are three groups of pathologic processes which may be operative in producing regressive changes. These are (*a*) inanition, (*b*) intoxication and (*c*) senility, and these may operate selectively not only on the nervous system as a whole but also on parts thereof. The first two of these may obviously operate on either normal or catagenetic soil. The third, however, when precocious always indicates catagenesis.

(*a*) Our knowledge of the ultimate nutritive requirements of the nerve cell is at present altogether too limited to enable us to place any of the degenerative familial diseases in this group as yet, but we do know from studies of the deficiency diseases that such selective inanition may occur in which the effect is largely or entirely on the nervous system (beri-beri). Such deficiency might logically result from faulty intake or from defective digestion or assimilation in the broadest sense. In the light of the nucleoprotein reduction in amaurotic family idiocy and of the fact that this process is not selective within the nervous system but involves all nerve cells, it is quite conceivable that it may ultimately find its place in this group. The familial cases of cretinism with developmental check on the growth of the brain may also fall here. Little of concise nature is known concerning the influence of dietary deficiencies in the pregnant mother on the development of the brain of the offspring, although this point is today open to a frontal experimental attack.

(*b*) Selective intoxication is used here in the broad sense, including both the effects of exogenous and endogenous toxins and the bacterial invasions. Selective poisoning of various parts of the central nervous system proves one of the most enticing as well as one of the largest experimental fields in neuropathology. We see many every-day examples of this selectivity—the action of wood alcohol on the optic nerve, of lead on the extensors, the selective localization of tabes and of poliomyelitis, etc. Kraepelin has laid emphasis on its importance in cerebral physiology, and much of the modern subject of pharmacology is built on this basis, in that what we know as the physiologic action of drugs is often a selective action not on the organ itself but on its nervous mechanisms. As an example of this, we may cite the action of digitalis on the heart by way of the vagus. In the hereditary groups of nervous and mental diseases, our knowledge of mechanization is too limited to permit of exact assignment here. Wilson, however, in his original description of progressive lenticular degeneration was evidently impressed with the possible explanation of the selective degeneration on the basis of toxic substances producted in the sclerotic liver.

3. Senility is an obvious corollary of the modern biologic view of a symbiotic but individual life for all the somatic cells of the metazoa. Many cells of the soma (this applies particularly to the essential functional cells in contrast to the supportive tissue or scar-forming cells) have gained a high adaptation for their special function at the expense of the faculty for regenerative nuclear division. Little if any multiplication of nerve cells takes place after birth. Selective senility, i. e., a shorter life period for some cells than for others in the same organisms, is readily demonstrable. Thus the early regression of the thymus and the involutional changes of the sex glands in both sexes are probably examples of early physiologic senile regression, while baldness, the loss of teeth and senile atrophy of the skin may also be cited as examples. Senile regression operating on the nervous system is in evidence in the cortex of practically all brains taken from aged persons. In my opinion, the distinct paling of the crossed pyramidal tracts, especially in the more distal segments in many cords from patients in the eighth or ninth decades, is more or less selective senile degeneration (Naka [27]) comparable to the earlier lateral scleroses.

Operating on a catagenetic nervous system, a selective precocious senility might well form the background of the heredodegenerations. The chronic degenerative lesions of these diseases are comparable to the cell scleroses of the senile period, although the absence of fatty degeneration products is inconsistent. Raymond [28] and Catola [29] sug-

27. Naka, K.: Arch. f. Psychiatrie **42**:604, 1907.
28. Raymond, F.: Lancet **1**:1859, 1908.
29. Catola, G.: Revist. di patol. nerv. **14**:224, 1909.

gested this precocious senility in the heredo-ataxias. Edinger [30] looked on them as a "using up" (Aufbrauch), and Bing [31] as the effect of wear and tear on a congenitally defective nervous system (abiotrophy in the sense of Gowers [32]).

One interesting fact coming out of a review of the hereditary and familial nervous diseases is the great predominance in the motor field. Thus the choreas, the dyskinesias, the spastic, atrophic and dystrophic groups on the motor side are in striking numerical contrast to optic atrophy and the ataxias on the sensory. Motor symptoms are obtrusive in our symptomatology and are therefore much more readily recognized than many of the sensory losses. Only two of the sensory systems, the optic and kinesthetic have so far been incorporated in the group. It would be interesting to know whether many cases of congenital and familial deafness or other sensory deprivations may not also belong here.

SUMMARY

1. The chronic heredodegenerations—progressive spinal muscular atrophy, familial spastic paraplegia, the hereditary ataxias of Friedreich and of Marie and their intermixtures and hereditary optic atrophy—are characterized by predominantly degenerative changes of the nature of cell sclerosis with little or no lipide degeneration. The ataxias are further characterized by coarse fibered tangled mats of gliosis unlike the columnar replacement of most tract degenerations.

2. The lenticular group is characterized by progressive degenerative changes associated with fatty degeneration and neuronophagia predominantly in the lenticular nuclei, with varying degrees of neuroglial response and usually—though not without exception—a striking hepatic cirrhosis. In Wilson's disease, the lesion is practically confined to the striate bodies; there is very little glial reaction, and cavitation results. In pseudosclerosis and bilateral athetosis, the lesions can also be found in other parts of the nervous system, and there is a glia reaction which results in some fibrous scarring and many giant multinucleated forms and pale vesicular giant nuclei.

3. The chronic choreas are characterized by extensive degenerations associated with fatty deposits of the striate body and with striking response on the part of both glia and connective tissue. In Huntington's chorea, the cortex is always involved, particularly in laminae II, III and IV in the central and frontal cortical fields.

30. Edinger, L.: Deutsch. med. Wchnschr. **30**:1633-1800-1921, 1904; 4-135, 1905.

31. Bing, R.: Deutsch. Ztschr. f. Nervenheilk. **26**:163, 1904.

32. Gowers, W. R.: Lancet, 1902.

4. Amaurotic family idiocy is essentially a dementia in which there occurs complete involvement of the nerve cells by a process leading to extensive distortion of cell form through the accumulation of débris. This débris is lipoidal (lipidal) but varies in its staining reaction to scharlach R and does not stain either by this method or with osmium as intensely as do the senile fatty deposits. The process is looked on as a disturbance of the intracellular metabolism, but whether of synthesis or catalysis cannot be determined.

5. Defects may be explained as simple failures in production of neuroblasts leading to numerical reduction but with comparatively normal form, as in microcephalia vera, or as deviations from the normal, as in the production of an abnormal brain pattern or cell lamination or as combinations of both processes. An explanation of "normal-looking" brains in strikingly defective cases is suggested on the ground of proportionate overgrowth of the supportive tissues with lack of either quantitative or qualitative development of the nerve cells or their interconnections.

News and Comment

DR. EBAUGH BECOMES PROFESSOR OF PSYCHIATRY AT UNIVERSITY OF COLORADO

Dr. Franklin G. Ebaugh, Director of Neuropsychiatric Department, Philadelphia General Hospital, has recently resigned to accept a position as Professor of Psychiatry, University of Colorado, and Director of the Colorado Psychopathic Hospital, Denver. He began his new duties on Dec. 15, 1924.

IMPORTANT SESSION OF LA SOCIÉTÉ DE NEUROLOGIE DE PARIS

Early next June, La Société de Neurologie de Paris will hold an extraordinary session. In the first place, it will hold its sixth Réunion Neurologique Internationale. In the second place, this session will be part of the celebration of the centenary of Charcot. This celebration is being organized by the Academy of Medicine, the Medical Faculty and the Neurological Society conjointly. In the third place, the Neurological Society will celebrate its own twenty-fifth anniversary.

Neurologists of all countries are invited to participate in this meeting and celebration. Those interested may address inquiries to Dr. A. Souques, 17 Rue de l'Université, Paris VIIe, France.

CORRECTION

In the paper by Dr. Mortimer W. Raynor on "Remissions in General Paralysis," which appeared in the October issue, the following corrections should be noted:

Page 422, fourth line, third paragraph, should read: "and died; fifty-nine were discharged as unimproved or improved and died;" page 427, the last sentence, Case 11, should read: "he died, August 22, 1920;" page 429, Case 16, third sentence, should read: "four months before admission, he had a slight injury of the head; gradually became indifferent, irritable and had periods of confusion;" page 437, Case 33, last line from bottom should read: "has maintained himself, although he has worked irregularly."

Abstracts from Current Literature

HISTOPATHOLOGY AND PATHOGENESIS OF TUBEROUS SCLEROSIS. MAX BIELSCHOWSKY, J. f. Psychol. u. Neurol. **30**:167, 1924.

There is no pathologic process in which malformations are so closely associated with new growths in one and the same lesion as in tuberous sclerosis. This disease, therefore, offers unusual opportunities for the study of the development of blastomas in general. Within the last few years, Bielschowsky had occasion to examine five new cases of tuberous sclerosis. In the course of this investigation, he found what had hitherto been only rarely observed, florid manifestations of growth in the ventricular tumors, which would ordinarily be regarded as clinically latent genuine cerebral tumors. He also found focal lesions in the cerebellar cortex—a rare finding.

Before discussing the pathogenesis of tuberous sclerosis, attention is called to a finding which is of special significance in the pathologic picture of the disease, namely, regularly regressing atypical large cells. These are found in the tuberous lesions in the hypertrophied convolutions as well as in the furrowed nodes; they seem to form large nests, and are equal in size to the normal Betz giant cells; rarely, however, they exceed the latter in size. Two varieties can be distinguished: one, with all the characteristics of highly developed ganglion cells; these cells usually have a vesicular shaped, chromatin-poor nucleus, and the cell body shows numerous well differentiated dendrites, and frequently markedly thickened neurofibrils as well as a rich chromatophilic substance (in stichochromic arrangement). They can be recognized as ganglion cells by their axis-cylinder projections which can be followed for great distances. The large cells belonging to the second variety present a homogeneous cell body; their shape varies a good deal, but is generally oval. Stained with the hematoxylin or Nissl stain, the cell body assumes a velvet-like appearance. The nuclei vary greatly in size and structure. Many cells contain several nuclei, some of which appear to be undergoing mitosis. These cells also have long dendrite-like projections, whose course is not as straight and as regular as that of the dendrites of genuine ganglion cells, but they show no axis-cylinder projections nor anything resembling axis cylinders. Although these cells show no actual evidences of being nerve cells, nevertheless they cannot be considered as neuroglia, because they never form glia fibers. Bielschowsky believes that it may be considered well established that these atypical undifferentiated cells are in the nature of a glial matrix. Some of the cells contain small cysts (vacuoles), while others have a rodlike structure arranged in the form of rosettes. Levi had originally regarded these cells as glioma cells. They are also found in neurinomatous plaques in the cerebral cortex and in the basal ganglia. Bielschowsky has no doubt that they are derived from spongioblasts, but does not believe in the genetic similarity or ambivalence of these two groups of cells. The variations in the two groups as noted in their finer histologic structure and in their topographic relationship to their surrounding structures of the cortex point to a different genesis of each group.

More recent investigations of tuberous brains, especially from younger persons, show (in serial sections) that ventricular tumors, heterotopies and cortical nodes are in some areas so closely associated with each other that there can be no doubt that there must exist some biologic relationship between them.

This cannot be appreciated unless serial sections of entire hemispheres are examined. Structurally, some of these brains resemble pachygyria and microgyria. This is significant because pathogenetically pachygyria bears a close relationship to microgyria, and, as the author has previously shown, certain portions of the cortex in tuberous sclerosis present definite evidences of genuine microgyria. Bearing in mind this relationship between microgyria and tuberous sclerosis on the one hand, and that between pachygyria and the latter disease on the other, one must necessarily assume that some dysgenetic factor in the sense of defective migration and differentiation of the neuroblasts is a potent cofactor in the genesis of the parenchymatous defects of the nodules in tuberous sclerosis.

The marked glial cells and glial fiber formation, as well as the frequent occurrence of glial proliferating centers in the form of cell nests with numerous cell divisions, all point to the correctness of the conception that the nodules of tuberous sclerosis represent a new growth formation of the gliogenous elements. The fact that these nodules are limited in their extent and do not tend to infiltrate surrounding structures and retain their benign character throughout the life of the individual, is a different matter. In this respect, they resemble the cutaneous and renal tumors, so that when one designates these nodules as central nevi, he well expresses their gross anatomic structure and their mode of growth. Just as in the case of the cutaneous nevi and renal tumors, the nodules of tuberous sclerosis may at any time become malignant and converted into richly cellular and rapidly growing tumors. Notwithstanding Pollak's views, Bielschowsky insists that the ventricular tumors constitute an essential component of the entire clinical picture. He also emphasizes the fact that the cerebral changes in tuberous sclerosis represent only one feature in the clinical picture and that the changes in the skin, heart, kidney, suprarenals and liver are of paramount significance in the pathologic definition and classification of the disease.

A study of the heterotopies and ventricular tumors in serial sections from cases of tuberous sclerosis shows that the migration and differentiation of the ectodermal elements begin relatively early in fetal life. The close relationship of the disease to pure malformations is evident. The formative insufficiency of the matrix and the lack of motility of the cells derived from the latter are common to both tuberous sclerosis and pure malformations; but in the usual types of malformation, developmental disturbances involve only neuroblasts; in tuberous sclerosis they involve in a similar, though more intense manner, the spongioblasts. The claims of previous observers that the glia in tuberous sclerosis is merely an expression of tissue reaction against the parenchymatous defect have not been definitely proved, although it must be admitted that the relationship between the parenchymatous defect and the spongioblasts is a much closer one than the author had previously believed. Whether the blastomatous degenerated glial areas are always accompanied by vestiges of poorly differentiated neuroblasts remains an open question, although there are even exceptions to this rule. Important, however, is the fact that the blastomatous degenerated glial tissue usually betrays by its localization its heterotopic character. These facts also explain the pathogenetic relationship between tuberous sclerosis and the central lesions of von Recklinghausen's disease. It has been definitely established that the central focal lesions in general neurofibromatosis are preeminently due to a lack of differentiation of the spongioblasts and to an inhibitory process which is manifested by a migration of these elements from the ependymal matrix and by the nature of their distribution in the affected tissues. The peripheral nerve changes in the neurinomatous form of

this disease also depend on the same principle of dysgenesis. Lack of differentiation and failure of migration of spongioblastic elements occurs also in other parts of the neuraxis presenting borderline states between malformation and neoplastic formation. Such is the case, for example, in the lesions of syringomyelia. Syringomyelia and tuberous sclerosis are not infrequently found in the same patient. Etiologically, tuberous sclerosis, von Recklinghausen's disease and syringomyelia have a common hereditary constitutional "anlage."

Little has hitherto been known of the cerebellar changes in tuberous sclerosis. Some authors have described large undifferentiated cells in the cerebellar cortex and in the white layer of the lamellae, but little can be found in the literature about focal lesions resembling those of the cerebrum. In only one of twelve cases could Bielschowsky find changes that could be detected macroscopically. These he reports in great detail, not only because of their rarity but because they are of great interest from the point of view of pathogenesis. The essential findings were localized lesions in the white substance of the basal cerebellar lobes that presented histologically the typical picture of tuberous nodes from the cerebral cortex. It must, however, be pointed out that there were some differences, such as in the greater amount of concrements in the cerebellar nodes as compared with those of the cerebral nodes. Secondly, there was a sharp limitation of pathologic from normal tissue; this is never seen in the nodes of the forebrain. It is this sharp limitation of the lesions in the cerebellum that gives them the appearance of genuine tumors. The cerebellar cortex directly over the "tumor" appears atrophic and sclerotic; the stratum granulosum is the only layer that appears normal, the external molecular layer being narrowed and almost entirely devoid of Purkinje and basket cells. In spite of these findings, the cortex presents nothing that can be regarded as characteristic of tuberous sclerosis; as a matter of fact, it resembles closely the cortex of advanced cerebellar atrophy in the heredo-ataxias and in juvenile paresis. On examining the cortex, one gets the impression that he deals merely with a marked diminution of parenchymatous tissue which has been replaced by glial proliferation. It is only the presence of a large cell here and there that makes the diagnosis certain. That the cortical sclerosis is not a secondary phenomenon or a sequel to a progressive parenchymatous degeneration but the product of a tuberous process, is evidenced by a peculiar heterotopy of the Purkinje cells which extends in the form of strands into the margin of the white lamellary and nuclear layers. The striking feature in the histologic picture of the case reported is that both phases of the tuberous process, the glioblastomatous and the neurocytodysgenetic, can be definitely distinguished from each other in spite of their close topographic relationship. In the cerebral lesions, in contrast to those of the cerebellum, both of these features seem to be united into one complex, which can be analyzed only with great difficulty. In this connection, Bielschowsky cites in detail Maas's case which was anatomically a definite case of von Recklinghausen's disease with focal lesions in the cerebellum that could be interpreted only as an expression of a "burned out" blastomatous process of the neuroglia; the adjacent cortex also presented evidences of a dysgenetic process which led to a displacement of the cortical layers. Although extensive focal lesions of a blastomatous character are rarely seen in von Recklinghausen's disease, Maas's case and cases reported by Nowicki and Orzechowsky, respectively, would seem to leave no doubt that as far as the cerebellar picture is concerned, tuberous sclerosis and von Recklinghausen's disease are histologically practically identical.

The final part of this most exhaustive study is devoted to a discussion of rapidly growing ventricular tumors. The histologic peculiarities of ependymal

tumors, especially their extensive petrification, would seem to justify the conclusion that we are here dealing with tumors whose growth energy has long ago been exhausted. Occasionally, exceptional cases are seen in which more recent lesions are found superimposed on the old lesions. Such cases have been reported by Kaufmann and Schuster, and more recently by Berliner and the present author. The latter's case was that of a 5 year old boy who was a low-grade idiot. He learned to walk at the age of 2, but could neither utter nor understand a single word; he was vicious, agitated and extremely dirty in his habits. He presented no signs of paralysis but had epileptic episodes in the form of brief attacks of vertigo and also typical convulsive seizures. The presence of general symptoms of increased intracranial pressure could, owing to the boy's mental state, not be determined. He developed a progressively increasing stupor, and toward the end he refused to take any nourishment. The attending physicians attributed his condition to a possible intracranial neoplasm. He had no sebaceous adenomas and no nevi. Necropsy showed at the base of both cerebral hemispheres numerous lesions of tuberous sclerosis. Many tumors ranging in size from a millet seed to a cherry were found on the lateral walls of both lateral ventricles. The left lateral ventricle was considerably dilated and showed on one of its walls, in addition to the nodules mentioned, a large neoplasm, of the size of a plum pit, which projected into the ventricular cavity. Careful examination of all the tumors showed that in addition to the typical ventricular nodules, there existed one tumor, which, owing to its rich blood supply and extensive nuclear and cell divisions, could be definitely distinguished from the smaller nodules. The histologic picture was undoubtedly that of a tumor in the nature of a blastomatous cell proliferation which was of more recent date. The tumor showed no such concrements as are regularly found in ordinary tuberous ventricular nodules. The absence of such incrustations is attributed by the author to the lively metabolic processes which must have been going on during the development of the growth. The microscopic findings are extremely suggestive of a flaring up of the same process which led to the origin of the small nodules during embryonal life. Whether this new growth began to develop on the basis of a previously existing old nodule, or whether it began as a genuine new growth is difficult to determine. The absence of concrements would seem to be in favor of the latter theory, whereas the fact that the structure of the new growth is identical with that of the ventricular nodules would again be in favor of the first theory.

Bielschowsky further points out that as difficult as the classification of these tumors may be, their histology and mode of development lend great support to Cohnheim's theory of the origin of tumors in general. The close relationship between heterotopy and tumors is nowhere as well illustrated as in the cerebral lesions of tuberous sclerosis. Heterotopy is formed by parts of the gray matter becoming fixed during embryonal life, so that, displaced as they are, they become partly or completely organized; as long as these parts adhere to the developmental direction of normal organogenesis, heterotopy results, but, as soon as they leave the normal direction of development and begin to grow, they give rise to tumor formation. As heterotopies may, however, also undergo unusually large development, it is extremely difficult to establish a sharp line of demarcation between these and tumors. Not all heterotopies possess the same tendency to a tumor "anlage." A study of the rapidly growing tumors of tuberous sclerosis definitely demonstrates one fact, and that is that spongioblasts and their derivatives constitute the blastomatous basic element in the development of heterotopy. Cells of this kind need not always be associated with neuro-

blasts; they may in the course of their development or during their process of migration become fixed heterotopically, or they may become damaged before reaching maturity, because maturation and migration run parallel to each other in all ectodermal cells of the neuraxis. This is especially noticeable in the histologic picture of von Recklinghausen's disease. We know now that mature glia cells are highly differentiated elements that surround with their plasma all parenchymatous elements, so that one can readily conceive that the arrest of their idioplastic differentiation may be compensated by an increased capacity for proliferation, and under certain conditions, as yet, unknown to us, they may lead to tumor formation.

All these facts lead finally to the question whether the findings in tuberous sclerosis do not offer a perspective for the genesis of cerebral glioma. It is undeniable that among the cerebral blastomas there exists one form which shows the closest relationship to the lesions and ventricular nodules of tuberous sclerosis. This type of tumor does not lend itself to definite classification; some designate it as a large cell glioma, others as a mixed cell sarcoma, and still others as a gliosarcoma. It is of interest in this connection to note that cases have been reported in which histologically some of these tumors showed in one and the same specimen features of neurinoma, ependymoma (Cash) and tuberous sclerosis. Although these facts are not sufficient to be considered as definite proof that glioma and tuberous sclerosis are the same type of tumor, nevertheless they are extremely suggestive, and would seem to point to the necessity of looking carefully in every case of glioma for dysgenetic manifestations in the tumor-free regions, with special attention to the possibility of finding abortive types of tuberous processes in the cortex and in the ventricular walls or in the ependymal proliferations—such as have been found in some cases of central neurinomatosis. This can only be accomplished by examining serial sections of entire hemispheres. Bielschowsky admits that studies of this kind are extremely trying and expensive, but he predicts that all efforts in this direction will be amply repaid, because it is the only way in which some of the obscure phases of the tumor problem may some day be solved. The paper is unusually well illustrated.

KESCHNER, New York.

ATYPICAL CHRONIC PROGRESSIVE DISEASE OF MIDDLE LIFE OF THE PSEUDOSCLEROTIC TYPE. HANS FIEISHHACKER, Ztschr. f. d. ges. Neurol. u. Psychiat. **91**:1 (June) 1924.

Spielmeyer showed that certain atypical cases of Wilson's disease are practically identical with the Westphal-Strümpell type of pseudosclerosis. In the same way, there are certain cases of pseudosclerosis that bear marked similarities to this disease, but that need clinicopathologic confirmation. The author presents in detail a case that clinically gave the picture of paralysis agitans and pathologically that of Wilson's disease, but differed from both in certain fundamental points.

A woman, aged 50, entered the hospital because of swelling of her right arm and hand since the age of 40. She had had measles as a child, smallpox at 14 and diphtheria at 24. She had had three abortions and six pregnancies. At the time of onset, her right hand became closed, and she had not been able to open it since. She had pain only in her finger tips. Seven years after the onset, she noticed weakness in her right arm and soon after weakness in her right foot also. Later, pains and tingling set in in both feet, especially on walking. For a year before entrance, the weakness in her right leg was so

great that she dragged her foot in walking. Tingling, numbness and tremors also appeared in her hands. About six months before entrance the patient had an attack during the night, characterized by general shaking, shivering, feelings of heat and cold and dizziness, but no vomiting. In the morning, she felt weak and noticed a stammering speech. Her right arm was much weaker, and so was her gait. For six months before entrance, her stools were numerous, and for three months after the foregoing attack she was incontinent. Her urine also was often passed involuntarily. Her memory was poor following her attack. She never had loss of consciousness or diplopia. Physical examination showed the left pupil to be larger than the right, the left side of the face smoother and weaker than the right, and the left spinal accessory nerve stronger than the right. The tongue deviated to the right and showed coarse tremors. The right forearm and hand were swollen, the right arm was held slightly flexed at rest; the right arm could be lifted only about 30 degrees, and then one encountered resistance and pain. The right hand was limited in all its motions, and was spastic. There was marked tremor of the right hand and forearm, especially of the thumb and index finger. The left arm was not spastic, but there was a coarse tremor present. The triceps reflex was increased on both sides, and there was also an intention tremor. The right leg showed spasm of the gastrocnemii. Abduction and adduction were weak on the right, but good on the left. Flexion at the knee was much weaker on the right. Dorsal flexion and plantar flexion of the right foot were weak. The knee reflexes were bilaterally increased. There was no Babinski sign or ankle clonus. Sensation was intact. In walking, the right leg dragged, the right knee hardly moved, and the right foot was strongly adbducted. The diagnosis was an atypical form of paralysis agitans. The patient returned after two years, complaining of continued vomiting and of stiffness in the left side.

She complained of severe pains in the left side of her body only. She had had a speech disturbance of a few days' duration. She now showed a left-sided Babinski sign and ankle clonus on both sides. Her condition was diagnosed this time as bulbar paralysis and she was transferred to another clinic. The interval history between her first and second entries states that she had sensations of fluttering before her eyes, felt as if she were filled with phlegm, and had paresthesia over the entire body. She could not open her right hand; her left was worse, and she could no longer walk. There was incontinence of urine and feces.

Examination revealed: bilateral foot drop, smooth and stiff facies, speech in a low monotone and inability to raise the shoulders. Other cranial nerves were intact. The muscle tone was increased in both arms, more so on the right. The right arm was flexed at the elbow and adducted, and the right hand was clenched. The left hand was held in the position of writing. There was no tremor at rest, but on motion there occurred a coarse tremor, which ceased after a few seconds. The reflexes were bilaterally increased in the upper extremities. The muscle tone in the legs was increased and resisted passive motion. The legs were held in slight adduction and outward rotation; the knees were slightly bent; the feet were strongly plantar flexed. Reflexes were bilaterally increased, more so on the right. In this clinic, no clonus or Babinski sign was found. After several months in the hospital, the patient died of pneumonia. During her stay in the hospital, the patient was seen by numerous neurologists, among others Oppenheim, and doubt concerning the diagnosis of paralysis agitans never arose.

Postmortem examination revealed a slightly thickened pia, without evidences of inflammation. The Betz cells showed evidences of chronic changes, which were at times severe. The glia cells were increased in number, especially in the paracentral lobule. In the third and fifth layers of the paracentral lobule were found large cells described by Alzheimer as typical of pseudosclerosis. No marked vessel changes were noticed. Here and there a hyalin appearance of the media was noted.

Marked changes occurred in the neostriatum. Macroscopically, there was marked atrophy, especially in the putamen. In the putamen the lateral and upper two-thirds were especially affected. There was an almost complete absence of the large ganglion cells, and those still remaining showed marked degenerative changes. The small ganglion cells were pretty well preserved in the lateral portions, but elsewhere showed atrophic changes. The small ganglion cells, however, showed much less change than the large cells. The glia was proliferated, corresponding to the cell loss. The vessels were relatively increased, their walls containing deposits of brown pigment, and their adventitial spaces being increased. The globus pallidus was better preserved than the putamen. The ganglion cells were relatively well preserved. On close observation, cells were found with slight or severe changes, but these were not numerous. The glia was moderately increased; here and there were small rodlike forms. The thalamus was normal.

In the lateral nucleus of the thalamus, the ganglion cells showed severe changes. The nuclei were compressed and torn, and the Nissl substance was irregularly distributed. Other cells seemed crumbled; others showed large nuclei, and still others showed marked chronic changes. The glia was proliferated.

The hypothalamic nuclei were normal. The corpus luysii was definitely smaller. The ganglion cells were lost in small focal areas. The nucleus ruber showed a diminution in cell content, and many cells showed thickened or bent cell processes. The glia was increased, with large nuclei.

The substantia nigra showed an intact zona reticularis, while in the zona compacta, a number of glia cells showed melanotic pigment. The dentate nucleus showed some chronically shrunken cells and others with a fine gitter-like network. The glia cells were slightly increased. The pons was relatively normal. The medulla oblongata showed intact twelfth nuclei, the ganglion cells of the inferior olive chronically changed and glia proliferation in the region of the vegetative nuclei.

The author first discusses the case from a clinical point of view. In favor of paralysis agitans are the attacks, the paresthesias, the central pains, the vegetative disturbances (edema hyperhidrosia and sphincter loss). The psychic features were the early loss of intelligence and the querulous attitude. He considers the onset at 40 early. Opposed to the diagnosis of paralysis agitans is the type of tremor described as a not quite rhythmical tremor of the right thumb and index finger and later of the entire hand. The static tremor with the fingers extended is coarse and irregular, and the tremor on the finger-to-nose test becomes almost a shaking tremor. The author feels that the coarse arrhythmical tremor points to Wilson's disease, and the similarity to the Wilson-Westphal-Strümpell type of disease is increased by the peculiar form of coordination disturbance in the legs and also by the rigidity. In favor of the diagnosis of Wilson's disease, the author finds the rigidity, the paralysis of the legs similar to the "pyramidalen Prädilektionsparese" and the increased

reflexes. The age of onset at 40 and the twelve year course would be against a diagnosis of Wilson's disease, but cases have been reported beginning late in life, and a familial disposition to the disease has been pointed out. Maas, Bielschowsky, and Bostroem have described cases occurring in later life without a hereditary disposition. Maas and Bielschowsky felt their cases to be cases of Wilson's disease. The author believes the case is not one of paralysis agitans. "We believe temporarily, at least, until the discovery of other more fundamental differential points . . . . that cases such as ours, as well, perhaps as those of Maas, Bielschowsky, etc., should be separated from the familiar Westphal-Strümpell-Wilson disease as an atypical group first occurring in later life, at least until the nature of "progressive lenticular degeneration" is better known.

In discussing the pathologic anatomy, the author points out that the entire brain is affected. The putamen is most violently affected, and the caudatum somewhat less, but neither pallidum, thalamus, the deeper layers of the cortex, or the cerebellum escaped unharmed. Pathologically, the differential diagnosis between paralysis agitans and Wilson's disease arises. For paralysis agitans we have a change in the globus pallidus as described above. The author concludes, however, that "despite certain outward similarities, the pathologic-anatomical process of our case differs from that of paralysis agitans in its localization as well as in its finer histopathology to such a degree" that the consideration of Parkinson's disease postmortem hardly is a possibility. He does not find a typical pseudosclerosis, the nucleus dentatus being intact, and the large glia cells described above not being the typical Alzheimer cells. On theoretical grounds, the case is probably not one of Wilson's disease because of the age of onset and the course.

The author discusses briefly the cases of Maas, Bielschowsky, Woerkom, von Economo and Schilders, and a few others which were similar in many respects to his.

ALPERS, Philadelphia.

THE ACTION OF ATROPIN AND OF CALCIUM ON THE VISCERAL REFLEXES. D. DANIELOPOLU, RADOVICI, AND A. CARMIOL, Rev. neurol. **30**:228 (March) 1923.

The studies in this paper, as well as in an earlier paper (Rev. neurol., 1922) were carried out on a patient with a transverse lesion of the cord at the level of the ninth dorsal segment. The visceral reflexes studied include the following:

1. *Cutaneous visceral*—contraction of pelvic viscera provoked by stimulation of the skin. It is more active if the tegument stimulated is nearer the nerve centers; e. g., pricking of the perineum presented the shortest latent period.

2. *Visceromotor reflex*—distention of the colon provokes movements in spastic paralyzed extremities.

3. *Oculo-viscero-motor reflex*—carried out by exerting light pressure on both eyeballs, manifests itself by contraction of the bladder (with expression of urine), movements in the colon, and movements of the spastic extremities.

The results of the experiments are charted in two tables—one for atropin and the other for calcium chlorid. Both were introduced intravenously. Atropin was used in two strengths: an "exciting" dose, 0.5 mg., and a "paralyzing" dose, 1 mg. The results obtained from atropin are briefly as follows:

1. The smaller dose, which excites the parasympathetic terminal nerve endings, exaggerates all the visceral reflexes.

2. The larger dose, which paralyzes the parasympathetic system, lowers and then finally causes the complete disappearance of all the visceral reflexes as well as the spasticity of the voluntary muscles.

For the purposes of an abstract, the table itself is probably most useful.

TABLE 1.—*Stein: Jan. 23, 122. Action of Atropin*

Time	Intravenous Injection of Atropin	Pulse	Contracture	Patellar Reflex	Reflex Viscero-motor	Reflex Oculo-vesical	Reflex Oculo-viscero-motor of the Abdominal Wall	Reflex Oculo-viscero-motor of the Lower Extremities	Reflex Cutaneo-vesical	Reflex of Defense of the Lower Extremities
Before	..	70	Active	Intense	Intense	Intense and rapid	Intense	Intense	Intense following the pricking of cutaneous area below the lesion	Intense
11:09	0.5 mg.	...	.....	.....	.....	.....	.....	.....	.....	.....
11:16	.....	88	.....	.....	Very active	Very active	Very active	Very active	Very active	.....
11:30	1 mg.	...	.....	.....	.....	.....	.....	.....	.....	.....
11:32	.....	132	Diminished	Diminished	Diminished	Intense	Diminished	Diminished	Obtained only by pricking the perineum; retarded	.....
11:40	.....	124	Very much diminished	Very much diminished	Absent	Definite but delayed	Very much diminished	Absent	.....	Diminished
11:45	.....	128	Very much diminished	Very much diminished	Absent	Definite but delayed	Very much diminished	Absent	.....	Very much diminished
11:52	.....	...	Very much diminished	Very much diminished	Absent	Diminished and retarded	Almost absent	Absent	.....	.....
11:55	.....	...	Very much diminished	Very much diminished	Absent	Diminished and retarded	Absent	Absent	.....	Very much diminished
12:00	.....	...	Very much diminished	Very much diminished	Absent	Diminished and retarded	Absent	Absent	Absent	Very much diminished
12:02	.....	...	Very much diminished	Commences to be very active	Reappears but feebly	Feeble and retarded	Feeble	Absent	.....	Very much diminished
12:20	.....	...	Very much diminished	.....	Very active	Active	Active	Absent	Weak, not obtained except by pricking perineum	.....

The Action of Calcium.—The authors have demonstrated in an earlier work that calcium chlorid, an amphotropic substance predominantly affecting the sympathetic system, produces at a certain dosage an inhibition of the movements of the abdominal viscera and a diminution of tone of voluntary muscle. These effects are due to the exciting action of calcium on the sympathetic nerve endings. Table 2 shows the results of the experiments. This table

TABLE 2.—*Stein: Jan. 29, 1922. Action of Chlorid of Calcium*

Time	Intravenous Injection of Calcium Chlorid	Contracture	Knee Reflexes	Viscero-motor Reflex	Oculo-vesical Reflex	Oculo-viscero-motor Reflex of Abdominal Wall	Oculo-viscero-motor Reflex of Lower Extremities	Cutaneo-vesical Reflex
Before	.....	Active	Active	Active	Active	Active	Active	Active
11:12	0.50							
11:15 / 11:20	.....	Active	Active	Active	Active	Active	Active	Active
11:29	.....	Diminished	Slightly diminished	Absent	Very much diminished and retarded	Very much diminished	Absent	Diminished, retarded, present only on pricking the perineum
11:31 / 12:17	.....	Very much diminished	Diminished	Absent	Absent	Absent	Absent	Absent
12:37	.....	.....	.....	Absent	... .	.....	.....	Weak, retarded; present only on pricking the perineum
12:47	.....	Partially returned	Well defined	Weak	Weak and delayed	Weak and delayed	Absent	Weak, but present on pricking the skin surface below the lesion

shows that the effects of calcium are the same as those of atropin in the paralyzing dose. Although the results of calcium and of atropin in a paralyzing dose are the same, the mechanism, on the other hand, is totally different.

Discussion of the Results.—The action of atropin on the visceral reflexes is easy to explain. The motor nerves of the abdominal viscera consist, in part, of the parasympathetic group. The small doses of atropin exciting the parasympathetic exaggerate the visceral reflexes, while the larger doses with a paralyzing action on the same nerves cause the reflexes to disappear.

The first visceral reflex which disappears after a paralyzing dose of atropin is the visceromotor reflex. For the effects on the other reflexes studied, the tables are sufficient. The earlier as well as the later studies of the authors lead them to offer certain views relative to the hypertonia of the viscera and of the voluntary muscles in transverse lesions of the cord. In their previous studies, they have shown that the pelvic viscera manifest an exaggerated contractility as contrasted with normal conditions. With the help of the diagraphic method, they have established the fact that the contractions of the bladder and of the colon are much greater in amplitude in diseased than in normal states. This they believe to be due to hyperexcitability of the parasympathetic system. This condition may be explained either on the basis of an excitation of the parasympathetic fibers, or more probably by a cutting of the sympathetic fibers at the level of the lesion which breaks the connection between the pelvic viscera and higher sympathetic centers. The second hypothesis is probably the correct one as regards the oculovisceral reflexes. The latter, where the cord is intact, are conducted by two pathways, sympathetic and parasympathetic and therefore produce both inhibitive and excitative effects. Where there is an interrupting lesion in the cord, these reflexes are apparently conducted by the parasympathetic pathway alone, and are excitative only.

They explain the phenomenon as follows: The sympathetic pathway of the reflex is intramedullary, and cutting or section of the cord prevents the inhibi-

tive reflex. The oculovisceral reflex can conduct itself only by the parasympathetic pathway which, in part, is extramedullary. It is composed of two superimposed reflexes: the first, through the eyeballs and along the path of the pneumogastric, provokes the contraction of the viscera supplied by that nerve; the second is released by contractions of the viscera and reaches across the cord as far as the pelvic viscera.

The authors' pharmacologic researches have led them to believe that the vegetative innervation is twofold: parasympathetic and sympathetic; so that as far as all the abdominal viscera are concerned, the parasympathetic is the activating nerve in the matter of tone and the sympathetic is the inhibitive nerve. Their studies have led them to believe that in paraplegia contractures, the parasympathetic endings are in a state of hyperexcitability, a phenomenon which, as in the case of all pelvic viscera, plays a part in the production of hypertonia.

All substances which increase muscle tone by exciting the parasympathetic (e. g., eserine, small doses of atropine, etc.), likewise increase visceral activity; likewise all substances which in certain doses paralyze the parasympathetic (atropin) or excite the sympathetic (epinephrin, calcium) diminish the hypertonia of voluntary muscle as well as the viscera.

It is possible that the voluntary muscular hypertonicity as well as the visceral may be due in part to interruption at the level of the lesion of the sympathetic pathways (inhibitive) which connect the lower segments of the cord to the higher sympathetic centers. This matter is still in the stage of being purely an hypothesis, and demands further study.

JONES, Detroit.

EXPERIMENTAL INVESTIGATION OF THE SO-CALLED "STICHLOCH-DRAINAGE" AFTER LUMBAR PUNCTURE, AS WELL AS ON THE RETENTION OF DYESTUFFS IN THE LUMBAR SACK. HERBERT STRECKER, Ztschr. f. d. ges. Neurol. u. Psychiat. **91**:114 (June) 1924.

Complaints of various sorts and even cases of death following lumbar puncture have been reported by various authors. This has been explained as follows: After the withdrawal of the cannula, a small hole (Stichloch) is left in the arachnoid and dura. It takes several days for this to close. So long as the hole is open, fluid can escape into the epidural space with the body in the upright position. This is called "stichloch-drainage." With the constant loss of fluid in this way, the water cushion of the brain is lost, and in this way, by pressure, more or less weighty complaints arise, and even cases of death have been reported. For the lessening of the stichloch-drainage some authors recommend the use of a small cannula, while others recommend the prone position for twenty-four hours after the puncture, with the feet elevated.

Ingvar reports three cases of death following stichloch-drainage after lumbar puncture. Jacobaeus, Frumerie and many others agree with him. Bungart, Weigeldt and others feel that the loss of fluid by stichloch-drainage is not of so great importance in the production of complaints after lumbar puncture, because they assert that the loss of fluid is soon compensated for by an increased production.

The theory of stichloch-drainage was first described by Baruch (1920), and he attempted to corroborate it by the following experiment: three cubic centimeters of a 2 per cent. indigo carmin solution was injected into the lumbar subarachnoid space; the cannula was left in situ, and was closed immediately after the injection with mandrin. In this way, a seepage of the colored fluid

from the lumbar sack was prevented. A permanent catheter was then placed in the bladder in order to be able to determine immediately the appearance of the dyestuff in the urine. In this experiment, no dye appeared in the urine after sixty-three minutes. The cannula was then removed, and eight minutes later the urine was colored blue. Baruch interpreted this experiment as follows: As long as the hole in the subarachnoid and dura was closed, no fluid could escape from the subarachnoid space. As soon as the cannula was removed, however, fluid escaped through the Stichloch, entered the subdural space, was taken up by the blood stream, and eight minutes later the dye appeared in the urine. Baruch believed that by this experiment he showed that there is actually a seepage or drainage of fluid from the Stichloch created by lumbar puncture. The author, however, points out that there is more than one pathway for the escape of cerebrospinal fluid into the blood stream, and asserts that even with the cannula in place, the dyestuff will appear in the urine after a time. The question, therefore, is not as Baruch puts it: If the Stichloch is plugged, does a discoloration of the urine appear or not? But it rather becomes: If the Stichloch is plugged, does the dyestuff appear in the urine more slowly or in lesser quantities than if the Stichloch were patent? The author attempts to answer this in a series of experiments.

The questions which the author attempts to answer in his experiments are these: 1. When and in what quantity is the dyestuff excreted in the urine if it escapes only by the physiologic pathways? The Stichloch is plugged in this experiment.

2. When and in what quantity is the dyestuff excreted in the urine when besides the physiologic pathway there is also the artificial way of escape through the Stichloch? If the dyestuff appears more quickly and in greater quantities in the second experiment than in the first, then we have good evidence in favor of stichloch-drainage. The author performed experiments with the cannula in situ and with the cannula withdrawn, in the same patient. Several weeks were allowed to elapse between the first and second experiments. Lumbar puncture was performed in the usual way; 1.5 c.c. of fluid were withdrawn and a 0.4 per cent. solution of phenolphthalein was injected into the spinal canal. In one part of the experiment, the cannula was left in place, and in the other, it was withdrawn. A permanent catheter was placed in the bladder. The urine was tested every five minutes for evidences of the dye, and quantitative determinations made in the Autenreith colorimeter. The cannula was left in situ only three hours, although it takes from ten to twenty hours for the dye to be excreted in toto in the urine.

The results of the experiments may be stated as follows: 1. The shorter the time the cannula remains in situ, the earlier the dyestuff appears in the urine.

2. The shorter the time the cannula remains in situ, the greater the amount of dyestuff excreted.

3. The shorter the time the cannula remains in situ, the less is the total amount of dyestuff in the fluid, i. e., the more dyestuff has escaped from the fluid. This would seem to indicate, therefore, that there is a greater excretion of dyestuff when the hole created in the arachnoid and dura is patent than when it is closed. The author concedes the possibility of a drainage of fluid through the Stichloch. He points out, however, that the recovery of the dye in the urine does not give one a clue as to the amount of fluid lost, and remarks that if the loss of fluid by drainage were as great as the supporters of the theory believe, we should get much more serious symptoms than actually occur.

In the second portion of his paper, the author deals with the question of the retention of the dyestuff in the spinal fluid, and tries to draw some conclusions as to the circulation of the fluid. In six cases, lumbar puncture was repeated three hours after the injection of the dye. The spinal canal was drained, and the specimens collected in separate tubes in quantities of 10 c.c. each. Determinations were made in the colorimeter, and fractional studies were made of the quantity of dye in each portion of fluid withdrawn. It was found that in the first hours after injection of the dye, most of the dye was in the lower portion of the lumbar sack, and at this time only small quantities of dye were to be found in the cerebral fluid. In the course of time, however, the dye became disseminated through the fluid, and appreciable quantities were found in the cerebral fluid, although clear differences can be found in the various portions of the fluid. To cite one experiment: One hundred and thirty-five cubic centimeters of fluid were removed. The entire quantity of fluid contained 47 per cent. of the dyestuff present, and the last quarter contained 9 per cent. Other experiments were performed to show that the amount of dye found in the fluid gradually decreased the greater the amount of fluid that was withdrawn; that is, the higher the situation of the fluid, the less dye was present. The only conclusion which the author draws is the fact that fractional dye studies give one a good insight into the physical relations of the cerebrospinal fluid. In an attempt to explain the reason for the greater quantity of dye in the lower portion of the spinal subarachnoid space, the author points out that the lower portion of the spinal sack is much larger than the cisterna magna, and therefore contains more fluid. Hence if the specific gravity of the dye is greater than that of the fluid, the lower portions of the fluid will naturally contain more dye than the upper portion.

ALPERS, Philadelphia.

THE IMPORTANCE OF THE RED NUCLEUS IN POSTURE. R. MAGNUS and G. G. J. RADEMAKER, Schweiz. Arch. f. Neurol. u. Psychiat., Festschrift für Constantin von Monakow **13**:408-411, 1924.

Monakow has said that the nucleus ruber, in common with its representation in the frontal lobes and in the cerebellum, is related to regulatory movements, particularly those concerned with the unconscious orientation with respect to the body and its relations to space, just as the rolandic region, with the pyramidal tract and its subordinate spinal centers, is concerned with the development of finer purpose movements. One must necessarily think of the continued effort required to maintain man and other primates in the upright position.

Magnus showed previously that an animal with a normal midbrain differs from a decerebrate animal by the absence of decerebrate rigidity and by the presence of normal posture. These investigations showed further that in a rabbit following a section which passed through the center of the right anterior quadrigeminal body and through the posterior third of the left anterior quadrigeminal body above, and through the pyramids just posterior to the corpus mammillare below, the postural reflexes remain normal, and no rigidity results. It was shown, furthermore, that the postural neck reflexes are mediated through centers which lie farther caudad than those serving other postural reflexes.

The location of these centers is now being investigated further by experimental work on cats and rabbits, as apes show too much evidence of diaschisis.

In one rabbit, a frontal section was carried through the midbrain in such a fashion that the tip of the oculomotor nuclei, in which the pupillary and accommodation centers are located, was removed. All reflexes concerning the external ocular muscles were preserved. Section just anterior to the trochlear nuclei did not disturb the reflexes of the superior oblique muscles. A number of sections were carried through different levels of the brain stem, and the behavior of the labyrinthine and postural reflexes was studied. It was found that when the section was performed anterior to the red nucleus, there was no decerebrate rigidity, and the labyrinthine reflexes relative to the position of the head, remained normal. On the other hand, all sections which injured the red nucleus produced decerebrate rigidity and abolished the labyrinthine postural reflexes. It was concluded that the centers for these reflexes were located in the region of the red nucleus.

In order to determine whether the red nucleus itself played the essential rôle in this connection, more accurately localized operations had to be performed. To carry out this plan, sections were performed by puncture along the median line, so as to sever Forel's decussation, which carries most of the efferent fibers passing from the red nucleus to the cord. These experiments were performed on rabbits in which the cerebrum previously had been amputated just anterior to the thalamus. After this preliminary operation, it was found that tonus and postural reflexes remained intact. When a puncture was made in the midline of the ventral surface, 2.5 millimeters deep, at the level of Forel's decussation, it was found that the postural reflexes were maintained, and there was no decerebrate rigidity. However, in a puncture 3.5 mm. deep, the labyrinthine postural reflexes were abolished, and decerebrate rigidity ensued. Serial sections were prepared, and these showed that in case of the 2.5 millimeters puncture, Forel's decussation was not reached, whereas following the 3.5 millimeters puncture, it was found to be completely sectioned, without noteworthy injury of the surrounding structures. Wernekinck's commissure remained entirely intact. Punctures from the dorsal side apparently had the same results, although these sections have not yet been studied completely.

It follows, therefore, that isolated section of the greater part of the efferent fibers of the red nuclei produces decerebrate rigidity and abolishes the labyrinthine postural reflexes.

It was also attempted to destroy both red nuclei by symmetrical punctures carried in from the sides of the midbrain. Two animals were completely studied. In one, there was decerebrate rigidity and absence of labyrinthine postural reflexes. In this case, it was found that the most anterior small cell portions of the red nuclei remained intact, while the large cell posterior portions were completely destroyed. In the second animal, the results were negative since the red nuclei had not been injured.

WOLTMAN, Rochester, Minn.

RHYTHMICAL CONVERGENCE SPASM OF THE EYES IN A CASE OF TUMOR OF THE PINEAL GLAND. J. R. DEMONCHY, Brain **46**:179 (July) 1923.

The author reports the case of a child, aged 14 years. The past history was negative. In December, 1919, he began to look ill and to complain of headache, dizziness and a singing noise in his left ear. In January, 1920, he had violent headaches, loud singing in his ears and a temperature of 40 C. (104 F.). His temperature became lower, but he remained ill and developed a squint. He became unduly sleepy, and sometimes slept all day. He came under observation in September, 1920.

Physical examination revealed a short, broad-shouldered boy. He was flabby, and there was a marked deposition of fat around the breasts and abdomen. Vision was ¾ in both eyes. The visual fields were concentrically limited to a slight degree, and there was a papilledema in both eyes — 3½ diopters on the right and 4 diopters on the left. The pupils were equal and regular; the reaction to light was slight in the right and absent in the left eye. The reaction to accommodation was good. "There was a convergent strabismus, which increased and decreased suddenly at intervals, so that a rhythmical spasm of convergence ensued. The converging phase of this movement was rapid, the diverging phase slower. The right eye moved fully into the outer canthus, the left eye not so much." There was a diplopia with the red-green spectacles.

The right masseter and temporal muscles were weak, and there was slight paralysis of the right side of the face. The jaw reflex was diminished. Speech was impeded, slow and scanning. The head was continually moved in a slight, irregular motion. There were incessant, small, irregular movements of both arms while at rest, and involuntary movements on motion which produced a form of intention tremor.

Muscular power was poor. The tendon reflexes were equally diminished on both sides. Sensation was normal. The legs were never still. Laboratory examinations revealed no albumin or sugar in the urine, a negative blood Wassermann test, 40 cells per cubic millimeter in the spinal fluid, and a spinal fluid pressure of 50 cm. of water.

The diagnosis was an inflammatory process or tumor involving the corpora quadrigemina. The facts leading to this diagnosis were: the conjugated paralysis of upward and downward movement of the eyes, Argyll Robertson pupils, motor and static unrest, disturbance of equilibrium in standing and walking, and somnolence. In addition, there was a tendency to adiposity and a small development of the penis and testes. This was considered to be secondary to distention of the third ventricle.

Necropsy revealed a tumor the size of an almond at the place where the falx and the two halves of the tentorium cerebelli join. There was an internal hydrocephalus with a distention of the third and lateral ventricles. A tumor the size of a nut was found at the epiphysis and the corpora quadrigemina. This extended dorsally and bent around the splenium of the corpus callosum, connecting with the tumor described above. Microscopic examination of the tumor showed it to be a mixed tumor of the terato-adenoma type. The hypophysis and other internal glands were not examined.

The author discusses more fully the convergence spasm. The deviations described above resembled a nystagmus of a medium degree. The frequency of the oscillations, however, were fewer than those of a nystagmus — one or two a second — were not regular, and were best seen with the patient looking straight ahead. Was there spasm of convergence or paralysis of divergence? This was not decided. The occurrence of a dystrophia adiposogenitalia instead of a macrogenito praecox which is characteristic of epiphysial disease is attributed to pressure on the hypophysis through dilatation of the third ventricle.

ALPERS, Philadelphia.

THE STRIAE ACUSTICAE. AN INVESTIGATION OF THE ANATOMIC CONNECTIONS OF THEIR FIBERS. OTTO MARBURG, Schweiz. Arch. f. Neurol. u. Psychiat., Festschrift für Constantin von Monakow **13**:419-427, 1923.

Von Monakow, Fuse and Ziehen have shown that a portion of the striae acusticae reach the cerebellum and may be designated as striae cerebellares.

Marburg, basing his views on the examination of a large number of normal, abnormal and fetal brains, formed the opinion that these striae constitute a fiber bundle passing from the corpus pontobulbare to the cerebellum. In a section of the medulla oblongata passing caudad to the tuberculum acusticum, a nuclear mass is seen, which is situated dorsolaterad to the corpus restiforme; this has been designated by Déjerine as the nucleus of the corpus restiforme, by Jacobson as the nucleus marginalis corporis restiformis, by Fuse as the nucleus parvicellulatus dorsalis, by Kaplan as the nucleus acusticus dorsalis, and by Ziehen as the nucleus tectorius. It is seen that there are as many names as there are authors. When these cells are traced caudad, they are seen to form a dorsal enlargement which comes in contact with the taeniae of the fourth ventricle and gives rise to a delicate band of fibers that pass caudad and mesad in a diagonal direction. They were designated by Retzius as the funiculus separans. They are essentially glial in nature, and they overlie a row of ganglion cells which impress one as being rudimentary. In only one place do these ganglion cells show any further development into a structure designated by Wilson as the nucleus postremus. This structure is constantly present in embryologic sections. Passing from behind forward, the accumulations of cells encountered may be designated as the nucleus postremus of Wilson, the nucleus subglialis of Ziehen, the marginal nuclei of the corpus restiforme, those noted in the taeniae, and finally the corpus pontobulbare.

Fibers are seen to arise from the corpus pontobulbare which pass ventrad, skirt the outer surface of the olive, pass over the pyramid with an indefinite relationship to the nucleus arcuatus, ascend in the raphé, cross the midline and reach the floor of the fourth ventricle. According to Kölliker, they pass around the nucleus eminentiae teretis or at times directly through it, where they are possibly interrupted in part. The bundles reunite and pass laterad on the floor of the fourth ventricle to the corpus restiforme.

The most lateral course of these fibers is extremely difficult to trace. They seem to end as though they were cut off. Macroscopically, however, it can be seen that a number of the more caudal bundles pass first dorsally over the corpus restiforme and then ventrally. A second path may exist, although this is not definitely proved, by which the fibers go directly from the corpus pontobulbare dorsal to the corpus restiforme, on the dorsolateral aspect of which they appear as though cut off. Marburg was able to find a continuation of a part of these fibers, which resemble the striae of von Monakow in that they pass over to join the dorsal fibers of the internal arcuate group. A third pathway was found which can plainly be seen to pass from the corpus pontobulbare with the pretrigeminal marginal group toward the median line, where some of them may be seen to cross.

These striae bring about a communication of the nuclei of the corpus pontobulbare with the cortex of the cerebellum. They pass either as external arcuate fibers around the olive and pyramid, cross in the raphé, and reach the floor of the fourth ventricle or as internal arcuate fibers through the substantiae reticularis to the raphé and the floor of the ventricle. Here they come in contact with the nucleus eminentiae teretis with which the contact is uncertain. Spiegel looks on this as analogous to the nucleus arcuatus. Whether these fibers have special functions or represent an ontogenetic rest of the pons cannot be determined; however, the latter view seems the more likely.

WOLTMAN, Rochester, Minn

THE SENSORY ACTIVITIES OF THE SKIN FOR TOUCH AND TEMPERATURE. DAVID WATERSON, Brain **46**:200 (July) 1923.

The current view of cutaneous sensation regards the skin as a "mosaic of tiny sensorial areas each sensitive to a specific stimulus, and the range of ascertained sensitiveness includes the sensation of touch, pain, cold and warmth" (Sherrington). This conception has led to the belief in the existence in the skin and subcutaneous tissues of specific structural mechanisms, each subserving one or other form of sensibility, whether of touch in the form of Paccinian and Meissner's corpuscles, or of cold and warmth, for which other forms of end-organs have been stated to act as receptors. Histologic examination, however, of such spots known to be sensitive to special stimuli has failed to demonstrate the presence of specific end-organs. Head and Rivers recently propounded their theory of a dual mechanism of cutaneous sensation, the epicritic and protopathic, but they deny the existence of a punctate mechanism for all forms of sensation, for in writing of temperature sensation they say that "in the normal skin the hot and cold spots are nothing more than minute areas peculiarly sensitive to either hot or cold, set in a territory over which temperature stimuli can also be appreciated." So that the existence of special receptors and special nerve fibers for touch, pain, heat and cold cannot be considered to be proved.

In a study of touch and its receptor, the author came to the conclusion that the epithelium of the skin is the receptor organ for the sensation of touch, performing the function of transmitting the stimulus excited by touch to the nerve terminals which are found among the cells of the deeper layers.

In a study of temperature sensations, the author came to the conclusion that: 1. There is a great difference in the number of cold and warm spots that can be detected over a given area in different persons. 2. The sum total of the spots elicited by a number of investigations is vastly in excess of that found at any one time, and therefore of the spots capable of giving the thermal sensation, only a fraction are active at one time. 3. The spots are readily exhausted by a repetition of the stimulus, and dulling of one spot is accompanied by the awakening to thermal sensibility of an adjacent spot.

The explanation which the author gives for these phenomena is given in the following conclusions: "The punctate distribution of sensitive spots found at a single examination is explained by the view that in the skin there is a constant coming and going of activity of the different parts. Other examples of 'fluctuation' are afforded by the skin capillaries in normal and in certain abnormal conditions, and the same principle may form the explanation of the variations found in areas of hyperesthesia and anesthesia."

ALPERS, Philadelphia.

CONCERNING THE RELATION OF THE CLAUSTRUM TO THE NUCLEUS AMYGDALAE AND TO THE AREA PIRIFORMIS, AND ESPECIALLY TO THE TRACTUS OLFACTORIUS. E. LANDAU, Schweiz. Arch. f. Neurol. u. Psychiat., Festschrift für Constantin von Monakow **13**:391-400, 1923.

The older authors considered the claustrum as an independent nucleus. Brodmann introduced the view that the claustrum is an integral part of the cortex of the island, just as the band of Vicq d'Azyr is characteristic of the visual cortex and the Betz cells of the motor cortex. He looked on it as a cellular layer split off from the innermost layers of the lamina multiformis (VI). Ariën Kappers' belief is essentially the same.

Landau does not think that this interpretation rests on a sound basis. Even gross anatomic sections, treated with iron sesquichlorid, show that the claustrum is by no means equally thick throughout its extent, that in many sections it extends far beyond the base of the island, and that it enters into relationship with the rhinencephalon or the amygdaloid nucleus. On the results of careful study of extensive adult and fetal, normal and pathologic, human and lower animal material, he became convinced that the claustrum bears no close relationship to the cortex of the island. The claustrum does not underlie the most anterior portion of the island. It is closely related to the amygdaloid nucleus. In frontal sections of the human fetal brain of six months, the claustrum is found to be one-third longer than the island and is more closely related to the putamen than to the cortex. In a microcephalic brain, otherwise apparently normal, it was found that the claustrum extended far above the upper margin of the island, particularly on the left; it did not quite reach the lower margin of the island, particularly on the right. If the claustrum were derived from the cortex, then the extent of the two should certainly correspond. In a hydrocephalic brain of six years, in which almost all structures, except the basal ganglia, had been destroyed by the pressure, the cerebrum resembling an empty sack with walls from 1 to 5 mm. thick, a fairly well developed claustrum appeared under the putamen. In a porencephalic brain of 50 years, the entire island was found to be missing on one side; however, the claustrum was well preserved. In view of these observations, the assumption that the claustrum is part of the deepest cellular layer of the lamina multiformis of the island is placed in doubt.

There seems to be no objection, however, to look on the claustrum as a gray nucleus entirely independent of the cortex of the island. Landau pointed out as early as 1918 that the claustrum is closely related to the substantia perforata anterior on the one hand and the nucleus amygdalae on the other. The relation of the claustrum to the substantia perforata anterior is particularly intimate where the olfactory bundle of the anterior commissure passes to the substantia perforata anterior and where the claustrum meets the olfactory tract. The small stria olfactoria medialis can always be found where the substantia perforata anterior comes in contact with the claustrum. The stria olfactoria lateralis passes to the base of the claustrum.

WOLTMAN, Rochester, Minn.

PATHOLOGICAL LAUGHING AND CRYING. S. A. KINNEIR WILSON, J. Neurol. & Psychopath. **4**:299 (Feb.) 1924.

As here considered, the terms pathologic laughter and crying are applied only to cases resulting from organic disease. Two forms are discussed: attack of tears or laughter, and paresis of the facial muscles for emotional expression without loss of volitional power over the same muscles. Cases are described to illustrate the occurrence of these phenomena in double hemiplegia, pseudobulbar paralysis, hemiplegia, disseminate sclerosis and degenerative conditions in the region of the basal ganglia. The pathologic emotional expression occurs in response to inadequate stimuli, often does not correspond to the actual state of feeling experienced by the patient and is frequently invariable as to type of emotion expressed, regardless of the nature of the stimulus. Experience suggests that the emotion expressed is usually laughter in disseminate sclerosis, tears in arteriosclerosis, and may be either one or the other in pseudobulbar paralysis. Consideration of the bearing of these

cases and others published in the literature on the James-Lange hypothesis leads Wilson to the conclusion "that the bodily reverberation, as James calls it, is not *per se* the emotion; the latter is not, so to speak, the mental symptom of the former."

Wilson then discusses the mechanism of emotional expression and points out that two factors must be considered—the faciorespiratory or skeletal and the visceral. The activity of each is reversed in sorrow as compared with that in joy. Study of many pathologic cases of interference with facial movement is convincing that the facial movements are not essential to experiencing emotion; further, the conclusion is drawn that "only when the psychical component is fused with the appropriate visceral component can emotion be felt acutely, and the latter is less significant than the former."

As the conclusion of his observations, Wilson suggests that there is some faciorespiratory mechanism, mainly reflex in character, possibly served by a supranuclear center linking the nucleus ambiguus with the phrenic nuclei. This center may be assumed to lie in the pons. Furthermore, there is a double cortical control of the faciorespiratory synkinesis. The first is actuated through the geniculate bundle of the pyramidal tract. Lesions of this bundle, especially if bilateral, will impair volitional control and thus release the involuntary control; the more marked the volitional loss, the greater will be the abnormality in the involuntary activity. Basing his conclusions on the work of Graham and of Spencer, Wilson hypothecates the existence of a second or involuntary corticifugal path to the faciorespiratory centers, independent of the voluntary corticopontobulbar tracts.

SINGER, Chicago.

UNUSUAL DISTURBANCES OF THE PERSONALITY. JOHANN SUSMANN GALANT, J. f. Psychol. u. Neurol. **30**:270, 1924.

Personality disturbances are difficult to explain at times. The term depersonalization has been especially difficult for Bleuler to define, as various men use the term differently. As a rule, personality changes are the result of disturbances in the ego, the ego being made up of numerous engrammes and psychisms. According to Galant, one may divide the personality changes into two large groups: disturbances of the ego (self-consciousness) and disturbances in the reactions and behavior of the personality. In the latter group, the disturbances are well recognized and fairly constant, as noted in hysteria, catatonia, paranoia, mania and the like. In disturbances of the ego, a more protean condition presents itself. If the individual fails to perceive himself as an entity and considers himself as something foreign, the change of personality becomes profound and difficult to analyze. When the disturbances of personality are additive, subtractive or transitive, one is usually able to work out the analysis. In the transformation of the personality, a much more serious disturbance is encountered.

Galant reports a most interesting case which shows marked transformation of the personality. The patient, a former teacher, in relating his experiences during the World War, stated that he was first a lieutenant in the Belgian Army. For his valuable work he was made commander-in-chief of all the King's armies; later he was made commander of the French armies, and because of his continued wonderful work he was made King of France, Italy, Austria and Germany.

The author calls this phantasy formation a depersonalization in contradistinction to dementia. The personality instead of going to pieces and being lost is transformed into a phantasy which does not come into conflict with the personality.

As a rule, these illusionary personality changes are transitory and of a Dämmerzustand type. Soon the patient wonders how he could have occupied himself with such a peculiar attitude and attempts to reconcile himself to his new situation. The author classifies this disturbance of the personality as the phenomena of the illusionary personality.

F. P. Moersch, Rochester, Minn.

Constructive Possibilities of a Mental Hygiene of Childhood. Bernard Glueck, Ment. Hyg. **8**:649 (July) 1924.

Glueck's article is an excellent summing up of the worth-while principles which psychopathology teaches concerning the problems of adjustment that face every child. Not the least virtue of his paper is to be found in the avoidance of mooted points of view, so that all those who are interested in the study of child life may read and profit, even though they entertain diametrically opposed theories as to basic mechanisms. For instance, scarcely any one would deny the tremendous influence of imitation in molding personality, or be unwilling to believe that in suggestion we have a powerful two-edged tool — constructive or destructive, according to how it is utilized. Nor again is the psychologic crisis which naturally arises in the life of the child, when power to control environment must gradually be relinquished, either to be denied or its great influence on personality growth to be controverted? These and similar situations are intelligently discussed. Furthermore, there is valuable information for the parent, the teacher and the social worker, which should at least stimulate a desire to understand the too often and too sadly misunderstood child. Even what is said about heredity should not offend the most rabid eugenist. The facts concerning the inheritance factor are not overlooked, but Glueck properly calls attention to the inability to predict personality and behavior on the sole basis of heredity. In other words, as Professor Jennings points out, we can never know precisely what kind of person the offspring of any two parents is likely to be. Perhaps the author has too great a tendency to separate the physical from the mental, the organic from the psychogenic. In the developmental life of the child, they are so commingled, both in their normal and pathologic significance, that this is scarcely feasible. However, probably Glueck wished to call attention to the overvaluation which from time to time has been given to minor somatic deviations.

Strecker, Philadelphia.

Further Studies Regarding the Nucleus Subputaminalis. Prof. Giuseppe Ayala, J. f. Psychol. u. Neurol. **30**:285, 1924.

Ayala, who has done a great deal of work on the basal nuclei, presents in this article a review of his studies on the nucleus subputaminalis. His work has been exceedingly careful, and while not entirely convincing, demands consideration from neurohistologists.

As early as 1911, C. Vogt emphasized the need of distinguishing the putamen from the globus pallidus and the classifying of the syndromes of these nuclei rather than speaking of them in a general manner under the heading of syndromes of the lenticular nucleus. Ayala, in accord with Vogt, carried out his investigations by doing a tremendous amount of histologic work employing serial sections of the brain (frontal, horizontal and saggital). He believes that he has isolated a nucleus which he designates as the nucleus subputaminalis.

In a frontal section at the level of the optic chiasm and in the region of the substantia grisea, a group of closely packed ganglion cells form this nucleus. A short ways distally at a level of the tuber cinerium, the nucleus enlarges and is directly lateral to the anterior commissure.

The form and extension of the nucleus subputaminalis is shown more clearly in horizontal sections which are taken directly through the globus pallidus at a level of the substantiae perforata inferior. Ten figures are employed by the author to show the general location and structure of this nucleus, but one may say that in man the nucleus is composed of a group of compact nerve cells which are situated ventrally to the border of the putamen and at the side of the anterior commissure.

In a group of eight monkeys (chimpanzee), the nucleus presented the same general location and histology. The author discusses the relationship of the nucleus to the surrounding nuclei, and while conceding a possible relationship, feels that the nucleus subputaminalis is distinct, even more so than the nucleus ansae peduncularis, and that this holds true for both man and monkey.

F. P. MOERSCH, Rochester, Minn.

THE DEVELOPMENT OF PSYCHOPATHOLOGY AS A BRANCH OF SCIENCE. BERNARD HART, J. Neurol. & Psychopath. **4**:334 (Feb.) 1924.

How far has psychology attempted to construct concepts that are based on experience, that resume that experience and are verifiable by an appeal to experience? The work of Charcot and Janet led the latter to formulate the conception of "dissociation of consciousness." This work has been amplified and confirmed by later observers and may be said to fulfil practically the conditions of a truly scientific formulation as laid down in the opening question. Freud has attempted the further step of determining "Why does dissociation take place?" The essential principles he has laid down are: "The series of phenomena which constitute conscious life and behavior are the result of the interaction of a number of psychological 'forces,' acting according to precise psychological 'laws.' Two or more forces may work harmoniously together, or they may conflict with one another. In the latter case an attempt at adjustment occurs, and certain of these attempted adjustments are of such a kind that morbid phenomena are produced, these morbid phenomena constituting the symptoms observed in certain forms of disorder."

But Freud has gone further and has built on these basic principles an elaborate structure in which are incorporated many further concepts. These, it is claimed, are based on "facts." But these facts are not directly observed and are the outcome "of a peculiar method, the method of psychoanalysis." The influences capable of acting as distributing factors in these observations are unfortunately "at any rate so far as our present knowledge goes, of an incalculable character." Such conceptions cannot, therefore, be said yet to comply with the requirements of science.

SINGER, Chicago.

THE ACTION OF TRICHLORETHYL AND ITS THERAPEUTIC APPLICATION. ERICH GOLDBERG, Deutsch. Ztschr. Nervenheilk. **82**:2 (June) 1924.

In 1916, while performing some experiments with trichlorethyl, Plessner observed that this drug apparently had some selective affinity for the sensory portion of the trigeminal nerve. He compared this action to radial neuritis

occurring in lead intoxication. According to Edinger, lead does not possess this affinity, but the frequent occurrence of radial involvement in these cases is simply due to the excessive use of these muscles innervated by this nerve.

Oppenheim suggested trichlorethyl in combating trifacial neuralgia. Plessner, Kramer and others reported favorable results. In 1921, Bieder experimented on rabbits, using large doses of trichlorethyl inhalations (up to 200 drops a dose) without any beneficial results but without any toxic manifestations. He believes that Plessner's toxic symptoms were not due to trichlorethyl, but to its decomposition into other products, especially carbon monoxid and phosgen. Trichlorethyl fumes to the eye produced a moderate conjunctivitis with a decrease of the corneal reflex. Direct injections into the sciatic nerve produced tissue changes even to necrosis as occurs with chloroform. Trichlorethyl fumes, furthermore, have an anesthetic on the nasal mucous membrane, and for that reason give temporary relief in trifacial neuralgia, provided it involves the second branch. Similarly, it is beneficial when used locally in the form of a liniment over other painful areas. It is superior to chloroform liniment in that it is less toxic and its anesthetic effects more prolonged.

HAMMES, St. Paul.

INTRACRANIAL BIRTH HEMORRHAGES. Editorial, J. A. M. A. **82**:394 (Feb. 2) 1924.

Ehrenfest (Am. J. Dis. Child. **26**:503 [Dec.] 1923) remarks that obstetricians have succeeded in revealing the exact mechanism in the origin of most of the more common types of cranial and intracranial lesions sustained by the child in the course of birth. Pediatricians also have made valuable contributions chiefly in regard to symptomatology. "They have discovered the evident etiologic relation of intracephalic birth hemorrhages to a reduced coagulability of the blood, rather frequently ascertainable in the newborn." There seems to be a widespread impression that the causation of intracranial birth hemorrhages often involves factors having no direct relation whatever to labor, and "the explanations may be summarized under the vague designation of hemorrhagic disease beginning in intra-uterine life." Ehrenfest believes that undue stress is being laid on the hemorrhagic diathesis, and that the widespread significance of both artificial, mechanical and physiologic trauma incident to birth is being overlooked. Careful postmortem examinations will frequently reveal unsuspected damage to the meninges and other structures.

ALPERS, Philadelphia.

Society Transactions

PHILADELPHIA NEUROLOGICAL SOCIETY

Regular Stated Meeting, Oct. 24, 1924

C. W. Burr, M.D., *President, in the Chair*

A Case of Jacksonian Manifestations with Preservation of Consciousness. Dr. Alfred Gordon.

A girl, aged 15, had a negative history except that at the age of 5 she had had a severe fall. About three months later, she developed epileptic seizures of the jacksonian type, the attacks being confined to the right side of the face and arm. Later the right leg became involved. At first, the convulsions occurred about two or three times a week, but they gradually increased in frequency. The fits consist exclusively of the clonic phase affecting simultaneously all the muscles. Until two years ago, each attack was accompanied by a slightly hazy mental state. Now there is no disturbance of consciousness and each attack is preceded by a sensory aura consisting of a tingling in the right arm. The clonic contractions are no longer present in the face but are confined to the right arm and leg. They are sudden in onset and termination, always followed by a sense of exhaustion, a mild paretic state in the right side and always witnessed by the patient.

Physical, laboratory and special examinations in every detail revealed nothing abnormal except that there was a marked nystagmus when the eyes were turned to either side.

Whether there is any relationship between the jacksonian fits and the trauma which occurred three months before the first seizure, is difficult to say. It is possible, however, that a meningeal or cortical cicatrix developed, following a small hemorrhage over the left motor area during the period between the head trauma and the onset of the fits. Another interesting feature of the case is the absence of tonic muscular contractions before the onset of the clonic contractions. This feature speaks against a subcortical lesion.

The Hemiplegic Form of Epidemic Encephalitis: Report of a Case with Recovery. Dr. Mitchell Bernstein.

Many clinical types of epidemic encephalitis have been described since von Economo's original description in May, 1917. The hemiplegic form of the disease is not frequently encountered, and in a statistical report of 864 cases of epidemic encephalitis collected by Wechsler, there were eighteen cases (2.1 per cent.) of this type. Buzzard and Greenfield were the first to call attention to this variety of the disease in 1919, reporting four cases, in three of which the diagnosis was confirmed by subsequent pathologic examination. McConnell recorded two cases; one, that of a man aged 52, who gradually developed a hemiplegia lasting one week, with recovery, and a fatal case in a woman aged 71.

Besides the hemiplegia which may occur at any time during the active stage of encephalitis or following the subsidence of the acute symptoms of this disorder, any of the other manifestations of encephalitis may be present.

Buzzard and Greenfield found petechial hemorrhages in the subcortical portions of the brain in their fatal cases. Vascular congestion, perivascular hemorrhages and massive hemorrhages may occur not only in the subcortical portions of the brain but also in the basal ganglions or in the cerebral peduncle, accounting for the hemiplegic symptoms.

The occurrence of hemiplegia during the course of a general infection associated with visual disturbances, pathologic drowsiness or periods of excitation, cranial nerve palsies, together with negative findings in the blood and cerebrospinal fluid, with no direct evidence of cardiovascular renal disease, should suggest the diagnosis of the hemiplegic form of epidemic encephalitis.

The following is a report of a nonfatal case recently observed:

An Italian woman, aged 36, the mother of three children, complained on awakening in July, 1923, of severe headache, vomiting and fever. The patient lay in a stupor for six hours. On the next day, vision was blurred, while the headache and fever continued. On the third day of the illness, active delirium occurred. She grew noisy and repeatedly struck her head in an effort to get relief from the unbearable headache.

The woman was well nourished. The pupils were equal, dilated and responded sluggishly to light; accommodation could not be determined. The chest, heart, lungs and abdomen were normal; the temperature was 101.2 F.; the pulse rate average 110 per minute, and the blood pressure was: systolic, 130; diastolic, 80. The extremities were extended, the left leg presenting a positive Kernig's sign and an exaggerated knee reflex. The Babinski reflex and ankle clonus were not demonstrable. There was no sphincter involvement. On the fourth day of the illness, the spinal fluid was under increased pressure. It reduced Fehling's solution. The Wassermann test, cell count and examination for organisms were negative.

The illness continued unchanged for two weeks when an abatement of all symptoms, except the visual defect, occurred for four days. During this period the patient insisted on getting up. On the eighteenth day, there was a return of headache and fever. The patient again became dull and drowsy. She could be aroused easily but would quickly lapse into a stuporous state. On the twenty-first day of the illness, the pulse rate decreased to 30 per minute; the blood pressure rose to: systolic, 160; diastolic, 100. Six hours later, the pulse rate was 90 per minute. The patient became very noisy.

A second lumbar puncture was performed on the twenty-third day of her illness, and the cerebrospinal fluid was again found to be under pressure. Fehling's solution was reduced. There were now 20 cells per cubic millimeter. No tubercle bacilli were found. The ophthalmologic examination at this time revealed an optic neuritis, together with a chronic chorioretinitis. Vision in the right eye was 10/200, while that in the left eye was 8/200.

On the twenty-fourth day of the disease, a palsy of the right side of the face and of the right leg was noted. The following day, the right arm became involved, together with loss of speech. Sensation was absent in the right side of the face and in the right leg. Both knee reflexes were diminished. The biceps and triceps reflexes were absent in the right arm. The sphincters were not involved. There were alternating periods of restlessness and stupor.

On the thirty-seventh day of the illness, there was a return of motion in the right arm and leg to a slight degree. The knee reflexes were now spastic, and ankle clonus and Babinski's reflex were demonstrated on the right. The first evidence of return of speech occurred on this day

On the fifty-fourth day of the illness (thirty days after the hemiplegia), the facial palsy had almost entirely disappeared. Speech was greatly improved, although still somewhat indistinct. An area of anesthesia along the ulnar side of the right forearm anteriorly and posteriorly and in the little and ring finger was present. The right knee reflex was normal, while the left was slightly exaggerated.

Eight months after the onset of the illness, the patient's only remaining difficulty was a slight slurring of certain words and a slight anesthesia of the ring and little fingers of the right hand. The altered mentality frequently observed as a sequel in this disorder was evidenced at this time by an attempt at suicide, apparently provoked by the annoyance of the slurring of words.

CLAUDICATION OF THE ANTERIOR SPINAL ARTERY. DR. BERNARD J. ALPERS.

A white man, aged 65, who worked as a night watchman, had complained of pain in the right leg and hip for fifteen years. The family history was negative for nervous and mental diseases. He had pneumonia at the age of 33, bronchitis every winter for the past ten years and varicose veins in his legs for the past fifteen years. At the age of 27, while in Ireland, he had some kind of venereal disease, having a sore and a urethral discharge, but he received no treatment.

His present illness began fifteen years before presentation, when he noticed pain in both hips, more on the right and radiating into the heels and feet and recurring at intervals of from two to three years. The pain first appeared in both hips but soon became localized almost entirely in the right hip. The pain was described as sharp, cutting, and at times lightning-like. It occurred at first at irregular intervals, and lasted from six to eight weeks, the first of which had to be spent in bed. Walking, sitting, or lying down on the right side usually increased the pain. During the past ten months, the patient had had the pain constantly until about eight weeks ago. During the past eight or nine months, the patient had had a feeling of weakness in his right hip and leg, and within the past six months also in his left leg. He did not walk as well as formerly, but his legs had never given way beneath him. During the last three or four months the patient had been conscious of twitching sensations in his legs.

General physical examination revealed a deviated septum, several carious teeth with marked pyorrhea, enlargement of the aortic arch with evidence of aortitis, sclerosis of the brachial and radial arteries, a blood pressure of 134 systolic and 80 diastolic, and huge varicosities of both thighs and legs, more marked on the left side. Cranial nerve examination revealed irregular and unequal pupils, the right larger than the left, reacting sluggishly to light. The other cranial nerves were intact. Marked fibrillary twitchings of the glutei and of the muscles of the thighs and calves were present. There was definite atrophy of the glutei on both sides of the posterior thigh muscles and of the muscles of the calves. The movements at the hip and knee joints were weak. The reflexes were hyperactive in the arms; the knee reflexes were active, the ankle and abdominal reflexes absent, and there was a questionable bilateral Babinski sign. Sensation was normal.

The blood picture was normal. The urine (a twenty-four hour specimen) was acid; it had a specific gravity of 1.018 and showed a trace of albumin. The renal function was 52 per cent. in two hours. The blood sugar, nonprotein nitrogen and urea, were normal; the blood Wassermann reaction was negative,

and the spinal fluid contained 2 cells; the colloidal gold, albumin, globulin and Wassermann tests were negative. Stool examination was negative. A roentgenogram of the dorsolumbar vertebrae showed a slight roughening and a tendency to lipping of the borders of the lower dorsal and upper lumbar vertebrae suggestive of an osteo-arthritis. Examination of the pelvis and hip joints was negative. All the teeth showed extreme pyorrhea and several root abscesses.

The case is by no means clear, but it has seemed to me that it could be best summarized on the basis of a vascular lesion which involved the anterior spinal artery in the region of the first lumbar to the second sacral segments, especially in view of the presence of a peripheral arteriosclerosis, and in view of the rather paradoxical physical findings. The latter seem to show the presence of a diffuse myelitis which apparently is vascular in origin. The presence of a varix of veins in the spinal canal cannot, however, be ruled out, although this condition is more rare than is a claudication of the spinal arteries.

The presence of marked fibrillary twitchings with definite atrophy would place the seat of the lesion in the anterior horns, and the history of a prolonged period of symptoms extending over fifteen years apparently indicates that the nature of the underlying process is probably vascular. There is a history of pain extending over fifteen years, typically sciatic in its distribution and nature, and only within the past three or four months a feeling of weakness and loss of power in the legs. It is possible that there has been a gradual closing of the vessel supplying the anterior horns, assuming that the lesion is due to a closing of this vessel and that only within recent months has the malnutrition of these cells been sufficient to produce a feeling of weakness and loss of power in the lower extremities. It is possible to explain most of the findings and symptoms which this patient shows on this basis. The loss of the Achilles reflex may well be due to the fact that the cells of the fifth lumbar segment are more involved than elsewhere, having atrophied to the extent of destroying the reflex arc. The involvement of the muscles of the buttocks, thighs and legs places the lesion in the region of the first lumbar to the second sacral segment, thus involving all the muscles of the lower extremities and leaving intact the anal and vesical arcs, as is the case with this patient.

It is difficult to explain the pain on the basis of a vascular lesion. On the other hand, the presence of huge varicosities in the lower extremities makes it seem possible that the same condition may exist in the vessels of the cord, and that pressure on the posterior roots by a varix of veins in the cord might produce symptoms of sciatic pain. The presence of a varix might also diminish the arterial supply to this region and might in this way account for the malnutrition of the vessels of the anterior horn, although this is probably better accounted for on the basis of a sclerosis of the vessel of the cord which supplies the anterior horns, namely, the anterior spinal artery. One must also consider the possibility of a varix within the sheath of the sciatic nerve on the right side producing pressure on the sciatic nerve and hence pain. It is likely also that the pain and the other symptoms and signs have more than one origin. Brissaud observed a form of intermittent claudication which was localized in the region of the nerve cutaneous femori and which was shown at necropsy to be due to vascular disease.

Déjerine first described the condition known as intermittent claudication of the cord in 1906. He described three cases with necropsy, mentioning as the essential features in the clinical picture the integrity of the peripheral

vessels, absence of vasomotor troubles, increase in the patellar and the Achilles reflex, and the presence of vesical symptoms in the form of imperative micturition. He was followed by Sollier, Foix and others who described similar cases. In 1906, Déjerine also reported a case of congenital spastic rigidity of the limbs in which the lesions were primarily in the blood vessels and were bilateral.

Spiller and Weisenburg, in 1903, reported a case of a man, aged 66, who showed partial paralysis of one upper limb resulting from a vascular lesion of the lateral column and anterior horn of the corresponding side of the cord. Their patient was well until three days before entrance into the hospital, when he was unable to use his right arm. Two weeks previously, he had had a fall. Examination showed a weakness of the right upper limb, and necropsy showed sclerotic blood vessels in the eighth cervical to first thoracic area, the sclerotic vessels being within the portion of the right lateral column adjoining the anterior horn. The walls of the vessels were very thick, and the anterior horn cells were much atrophied. The anteroposterior diameter of the right horn was smaller than the left.

Spiller, in 1909, reported a case of thrombosis of the cervical anterior median spinal artery. This case developed in a man who had had a "spinal meningitis" four years previous to his illness. His illness came on one day following the lifting of four blocks of ice weighing 100 lbs. each, a task which he had performed for many years. About fifteen minutes after lifting the last block, he felt weak and numb in the upper extremities, and fifteen minutes later he was weak and numb in the lower extremities. When examined, he had regained the use of his lower extremities, his patellar reflexes were exaggerated with a Babinski sign on the right side, pain and temperature sensation was impaired in the upper part of the thighs and as high as the first and second ribs. He had incontinence of the bladder and rectum, and he was almost completely paralyzed in the upper limbs. Necropsy showed a thrombosis of the anterior spinal artery and a thickening of the branches coming from it in the eighth cervical and first thoracic segments. The softening was intense in the eighth cervical and first thoracic segments, and even extended as high as the fourth cervical segments. The lesion implicated the anterior horns, the whole anterior part of the cord in advance of the crossed pyramidal tracts and the extreme part of the posterior columns. The pyramidal tracts were partly degenerated. Spiller concludes that "the case is extremely important in showing that thrombosis may occur in a very limited distribution of spinal vessels," and that "spinal thrombosis is not a rare condition, and is probably the cause of most of the apoplectiform palsies that occur in myelitis."

Preobrashenski describes a case of occlusion of the spinal artery which he thought was syphilitic in nature. Oppenheim says he has never seen a case.

While thrombosis of the cord vessels may be fairly common, telangiectasis is quite rare. Spiller and Frazier report the case of a woman, aged 25, whose symptoms were loss of power and severe pains extending over a long period. Cobb reports a case and collects six others from the literature, the outstanding symptoms being loss of power and pains of rather an acute nature, with sensory findings and increased tendon reflexes. The picture presented by our patient is more in accord with thrombosis of the anterior spinal artery, although it has symptoms which might be referable to a telangiectasis of the vessels of the cord.

DISCUSSION

DR. T. H. WEISENBURG: Dr. Ashhurst examined this patient and said that the varicose veins were possibly neoplastic and were the largest and most extensive he had ever seen. He saw no reason from the surgical point of view against the theory that there might be a similar varicosity in the vessels of the spinal cord. The level of the lesion seems clear because the fibrillary tremors and atrophy are below the waist line and not above. With the presence of atrophy, some loss of power and absent Achilles' reflex, the lesion is obviously between the levels of the eleventh dorsal and second sacral segments. A thrombosis of the anterior spinal artery best explains the symptoms, assuming of course that the thrombosis is incomplete in the upper level of the lesion but complete in the sacral segments, thus causing a necrosis of this level with consequent absence of the Achilles reflex.

DR. WILLIAM G. SPILLER: The presence or absence of the Babinski reflex would be of diagnostic value in intermittent claudication. It may be present in the spinal form but not in the peripheral form.

DR. ALFRED GORDON: Were electrical reactions of his muscles taken? Are reactions of degeneration present?

DR. BERNARD J. ALPERS: He had no reaction of degeneration. We could not demonstrate a Babinski reflex.

Book Reviews

BEYOND THE PLEASURE PRINCIPLE. SIGMUND FREUD, M.D., LL.D. Pp. 83. Price, $1.50. Second German edition; trans. by C. J. M. HUBBACK. New York: Boni & Liveright, 1924.

Psychanalysis lays no claim to priority and originality, but, in the absence of any philosophical or psychologic theory to explain the meaning of feelings of pleasure and pain, Freud unhesitatingly undertakes the construction of the most elastic hypothesis that can touch on this least penetrable region of psychic life.

He is skilfully and fairly his own critic, acutely aware that observation of facts and imagination may just as well lead ignominiously astray or to brilliant discovery. In an attempt at intellectual impartiality, he realizes difficulties attached to those so scientifically interested in the way of preferences which leads to speculation. He admits good grounds for distrust but looks for a tepid feeling of indulgence. He deplores the shortcomings of description because of the meticulous psychologic terms necessary to describe the psychology of the deeper layers. He borrows freely from biologic science, being especially fond of Weismann's theories of germ plasm.

Every mental process originates in an unpleasant state of tension and determines for itself such a path that will relax the tension with avoidance of pain or with production of pleasure. He considers pleasure and pain in relation to the quantity of mental excitation present, pain corresponding with an increase and pleasure with a decrease. The amount of increase or decrease in a given time is probably the decisive factor in feeling.

The psychic apparatus attempts to limit the quantity of excitement, and whatever operates in the opposite direction must be felt to be contrary to function and therefore painful. A strong pleasure tendency is present in the psyche, opposed by certain other forces or conditions. The first check on the pleasure principle is the influence of the instinct of the ego for self preservation, which replaces it by the reality principle. The latter, without resigning the intention of ultimate pleasure, forces its postponement and the temporary endurance of pain on the circuitous route to pleasure. In the matter of sex impulses, the pleasure principle commonly has the upper hand of the reality principle, much to the detriment of the whole organism.

Some of our inborn instincts are antagonistic in desires to others that can be welded into the comprehensive unity of the ego. These are split off by the process of repression, are retained at lower developmental layers and, for the time, deprived of any possibility of gratification. If they succeed, as easily happens in the repressed sex impulses, in forcing their way through to a direct or substitutive gratification, the success brings pain to the ego instead of pleasure. This process, which changes a possibility of pleasure into a source of pain, is not fully understood, but, he states, all neurotic pain is of this kind, it is pleasure which cannot be expressed as such. These sources of pain and other painful experiences do not call in question the supremacy of the pleasure principle, however, in the course of psychic processes.

Traumatic neurosis, the psychic reaction to external danger, clinically approaches hysteria in its motor symptoms, but usually surpasses it in its

strongly marked subjective suffering, resembling rather hypochondria or melancholia, and in the evidences of the far more comprehensive general weakness and shattering of the mental functions. The chief causal factor seems to be in the element of surprise in the fright. An injury or wound sustained at the same time generally tends to prevent the occurrence of the neurosis. Fright occurs in the presence of unexpected danger and contains the important element surprise. Apprehension is rather expectant of danger and protects against fright and, therefore, against the fright neurosis.

The dreams in traumatic neuroses repeatedly recount the disaster, terrorize the patient and help to cause a psychic fixation as to the trauma, as occurs in connection with hysteria.

Freud briefly reviews the changes in the aim of psychanalytic technic in the past twenty-five years. At first, it was directed toward divining the unconscious, of which the patient was unaware, and collecting its various components and communicating them to him at the right time. Therapy not being complete, the next aim was to compel the confirmation of the reconstruction through his own memory. The resistances were to be unveiled and explained, and by human influence—transference—he was taught to abandon them. The aim to bring into consciousness the unconscious was not fully attainable by this method. He cannot recall sufficient of the repressed, so has no conviction that the conclusions are correct. He is obliged to repeat as a current experience what is repressed, instead of, preferably, recollecting it as a fragment of the past.

When the sphere of transference is reached, i. e., the relationship to the physician, the earlier neurosis is replaced by the transference neurosis. This should be as limited in scope as possible in order to force the most into memory and to leave as little as possible to repetition. He must live through a certain part of his forgotten life, the physician seeing to it that some measure of ascendency remains, in the light of which the apparent reality is recognized as a reflection of a forgotten past. Conviction is thus obtained and with it the dependent therapeutic result.

The resistance proceeds from the conscious and subserves the pleasure principle in trying to avoid the pain that would be aroused by the release of the repressed material.

Repetition-compulsion not only occurs in the transference neurosis, but can be observed in apparently normal persons who have never shown signs of a neurotic conflict. It gives the impression of a pursuing fate, the endless repetition of the same. Freud assumes from these observations that there exists in the psychic life a repetition compulsion which goes beyond the pleasure principle. The dreams of shock patients, already referred to, and the play impulses of children are related to this compelling force, and he considers it to be more primitive, more elementary and more instinctive than the pleasure principle which is displaced by it.

Beginning with Chapter 4, Freud emphasizes that whatever follows is speculation and the exploitation of an idea. Consciousness cannot be the most general characteristic of psychic processes, but merely a special function of them. It has to do with perceptions of excitations coming from without and feelings of pleasure and pain derived from within the psychic apparatus. All excitation processes leave permanent memory traces which have nothing to do with the question of becoming conscious. He assumes consciousness and memory-trace to be processes incompatible with each other in the same system.

He allots a position in space, the cortex, in which the exciting stimuli become conscious but leave behind no lasting trace. All memory traces would come about in the next systems inward.

In the development of a theory of protection against stimuli, Freud imagines the living form as a simple undifferentiated vesicle of sensitive substance, with its surface, differentiated by its very position, serving as an organ for receiving stimuli. This living vesicle, floating around in a world charged with the most potent energies, would need for preservation some protection against the operation of stimuli. Such protection comes from the outer layer operating as a special, nonvital, inorganic integument, preventing the energies of the outer world from acting more intently than necessary on the layers immediately below which have preserved their vitality and are able to devote themselves to the reception of stimuli that have been let through. He considers the protection against stimuli quite as important as the reception. The sense organs are explained as originating from the receptive external layer. They operate for reception of specific stimuli, also as a fresh protection against overwhelming stimuli and for warding off unsuitable stimuli. They merely sample the outer world like antennae which touch and withdraw.

The sensitive cortical layer beneath the integument also receives excitations from within, but there is no possible barrier toward these, and they pursue their way direct and in undiminished strength. Certain characteristics of their course produce the series of pleasure-pain feelings which are preponderant over all outer stimuli. Inner excitations bringing overplus pain are treated as though acting from without so as to apply against them the defensive measures of the barrier. This is the origin of projection.

Stimuli strong enough to break through the barrier are called traumatic. An external trauma will call forth an extensive disturbance in the energies of the organism and will set in motion every protective device. The pleasure principle is put out of action. The psychic apparatus is flooded with masses of stimuli, and the task of "binding" the stimulus mass that has broken through presents itself that its discharge may be brought about.

Traumatic neurosis may be regarded as a result of an extensive rupture of the barrier against stimuli. Fright plays its part, too, due to the fact that the mechanism of apprehension has not made the proper preparation, including the overcharging of the stimuli receptor systems. These are, therefore, hardly in a position to "bind" the oncoming masses of excitation, and rupture and its consequences appear all the more easily. The apprehensive preparation, together with the overcharging of the receptive system, represents the last line of defense against stimuli.

Again referring to the dreams of the traumatic neuroses taking them back to the situation of the disaster, Freud concedes for the first time an exception to the principle that the dream is a wish fulfilment. He assumes that these dreams subserve another purpose, i. e., to restore control of the stimuli by developing apprehension, the failure of which to develop caused the neurosis. This purpose is preliminary to the aim of attaining pleasure and avoiding pain.

Anxiety and punishment dreams are no such exception for they merely put in the place of the interdicted wish fulfilment the punishment appropriate to it, and are thus the wish fulfilment of the sense of guilt acting on the condemned impulse. Dreams of the traumatic neuroses and those that bring back the recollection of psychic traumas of childhood obey the repetition-compulsion.

The most prolific sources of inner excitations are the so-called instincts. They are free-roving, striving for discharge, and it should be the task of the

higher layers of the psychic apparatus to "bind" the instinct-excitation. Failure to do so would evoke a disturbance analogous to the traumatic neurosis. Only after this successful binding could the pleasure principle and its modification, the reality-principle, come into sway without hindrance.

The expressions of a repetition-compulsion, both in the playful activities of children and in the experiences of psychanalytic treatment, show in a high degree an instinctive character. Accordingly, "an instinct would be a tendency innate in living organic matter impelling it towards the reinstatement of an earlier condition, one which it had to abandon under the influence of external disturbing forces." Instead of the factor urging toward change and development, we are required to recognize in instinct the very opposite, the expression of the conservative nature (regression) of living things. In heredity and embryology, we have the most imposing proof of the organic compulsion to repetition.

Freud's hypothesis, therefore, is that all organic instincts are conservative, historically acquired, and are directed toward regression, toward reinstatement or something earlier. Consequently, he is obliged to place all the results of organic development to the credit of external disturbing and distracting influences. In other words, the objective of organic striving is an ancient starting point, which the living being left long ago, and to which it harks back again by all the circuitous paths of development. "If we may assume as an experience that everything living dies from causes within itself, and returns to the inorganic, we can only say 'the goal of all life is death,' and, casting back, 'the inanimate was there before the animate.'"

At one time, the properties of life arose in a lifeless matter. The first instinct was to return to lifelessness. Death was easily within reach, probably due to a very short course of life. Through a long period of time, the living substance may have been constantly created anew and easily extinguished, until decisive external influences altered in such a way as to compel the still surviving substance to ever greater deviations from the original path of life and to evermore complicated and circuitous routes to the attainment of the goal of death. These circuitous ways to death, faithfully retained by the conservative (regressive) instincts, would be the phenomena of life as we now know it.

According to this speculation, the significance of the instincts of self preservation, power and self assertion shrinks to nothing. Freud's explanation is that these are part instincts, designed to secure the path to death peculiar to the organism, and to prevent any return to the organic other than immanent. The organism is determined to die in its own way.

In discussing the sex instincts, Freud says that not all the elementary organisms of the body of a higher form of life take part in the path of evolution to the natural end, i. e., death. The reproductive cells detach themselves from the parent, charged with all the inherited and newly acquired instinctive dispositions. Under favorable conditions, these develop and repeat the same cycle to which they owe their origin. They operate against the death of the living substance and win for it what seems to be potential immortality. Freud suggests that this only means a lengthening of the path to death.

A sharp contrast has now been established between the ego instincts or death instincts and the sexual instincts: one impelling toward death, the other toward preservation of life. Weismann is freely quoted as to the distinction of living substances into a mortal and an immortal half, the soma and the germ plasm. He draws an analogy with his own conception. Weismann

considers living substance morphologically; he, on the other hand, deals with the forces active in the living substance and distinguishes two kinds of instincts, i. e., those which guide life toward death (ego instincts) and the sexual instincts which effect the renewal of life. He calls this conception an apparent dynamic corollary to Weismann's morphologic theory.

But Weismann claimed potential immortality only for multicellular organisms, unicellular organisms having no germ-plasm. Freud calls attention to the experiments of an American—Woodruff—who cultured a ciliated infusorium, which reproduced by direct division. He traced the propagation to the three thousand and twenty-ninth generation. The last descendant was as lively as its original ancestor. This, no doubt, proves potential immortality of protozoa.

Two facts are emphasized as a result of biologic research. First: if the animalculae have the opportunity of mingling, "conjugating," afterward separating, they become "rejuvenated," this conjugation being the prototype of sexual propagation of higher animals; secondly, it appears that they are injured by the products of their own metabolism which bring about death. He suggests, further, that the death instinct might also be active in the protozoa, obscured by those forces tending to preserve life.

The question arises whether the protozoa can be credited with anything beyond what they exhibit, and whether it may be assumed that forces and processes which become perceptible in the case of higher animals first arose in the most primitive. Do life instincts operate in the simplest forms of life? Why else has conjugation, which makes the task of dying harder, been retained and elaborated? Death instincts must be associated with life instincts from the beginning.

It is briefly suggested that sadism is a death instinct which is driven apart from the ego by the influence of the narcissistic libido, so that it becomes manifest only in reference to the object. It then enters the service of the sexual function. The part instinct of masochism, the one complementary to sadism, is a recoil of the sadism on to the ego itself.

Science tells us so little about the origin of sexuality that the problem cannot even be penetrated by the ray of an hypothesis. He recounts a fantastic hypothesis—a myth rather than a scientific explanation, but something that fulfils the one condition for the fulfilment of which we are laboring; that is, it derives an instinct from the necessity for the reinstatement of an earlier situation.

He refers to the clue of Plato that at the time of its animation, living substance was divided into small particles, which since that time have been striving for reunion by means of the sexual instincts. Did these instincts—in which the chemical affinity of inanimate matter continued—passing through the realm of the protozoa, gradually overcome an environment charged with dangers to life? And did these dispersed fragments of living substance thus achieve a multicellular organization, and finally transfer to the germ cells in a highly concentrated form the instinct for reunion?

He adds that he does not know just how far he believes in the views set forward. This third step in the theory of instinct, i. e., the assertion of its conservative and regressive nature, its ancient goal of reinstatement, cannot claim the same certainty as the two former ones, the extending of the conception of sexuality and the establishing of narcissism. The theory of the regressive character rests on the facts of the repetition—compulsion—and he feels that perhaps he may have overestimated their significance.

In concluding, he considers the relation of the instinctive repetition processes to the domination of the pleasure principle. One of the most important functions of the psychic apparatus is to "bind" the instreaming instinctive excitations, and to transform their freely mobile energy into a predominantly quiescent charge. This transformation takes place in the service of the pleasure principle, and is an act of preparation which secures its sovereignty. On the other hand, the pleasure principle seems directly to subserve the death instincts. It keeps guard in particular over the inner increases in stimulation which have for their aim the complication of the task of living.

CLINICAL STUDIES IN EPILEPSY. COMPOSED OF CLINICAL NOTES ON SOME EPILEPSIES AS BEARING ON THE PATHOGENESIS OF IDIOPATHIC EPILEPSY. By DONALD FRASER, M.D., F.R.F.P. & S. (Glas.). Consulting Physician, Royal Alexandra Infirmary, Paisley; Member, Medical Advisory Board, "Colony of Mercy for Epileptics," Bridge of Weir; Consulting Physician, Paisley District Mental Hospital. Pp. 243. Price, $2.50. New York: William Wood & Company.

This is a somewhat peculiar but interesting book, and it contains a great deal of information about epilepsy. None of this information is original with the author. It is assembled from widely scattered sources, much of it practically forgotten. And it is to the credit of the author to have brought forward some of this forgotten or ignored lore, notably the thoughts and pronouncements of Hughlings Jackson.

But the title of the book is a misnomer. It is not the report of a series of careful clinical studies but a series of essays on various aspects of epilepsy, here and there illustrated by cases. And much of the matter is purely speculative.

The author states that the book is in effect the expansion of what was meant to be a journal article based on a single case of epilepsy. This case is an unusual and most interesting one and quite instructive, but even this one never was carefully studied by a physician. So far as the report shows, the patient was carefully examined only once, that time by Hughlings Jackson more than thirty years before. Dr. Jackson's report is most characteristic, hence a joy to read. Otherwise the case is in the main reported by the patient himself, an intelligent clergyman and graphic writer, and the treatment was "managed by himself mainly with an occasional hint from myself and others." In fact it would appear that this case (self) observed over a period of about thirty-three years and related in anecdotal style is a real contribution to the natural history of epilepsy.

Chapter II is on psychology and epilepsy. The author denies the psychogenesis of epilepsy and avers that "the psychology of epilepsy is the psychology of its postepileptic conditions."

Chapter III is on vasoconstriction and epilepsy and supports the idea that vascular spasm has a great deal to do with the epileptic seizure. The author says . . . "This morbid action of the cortex is the result of a toxin whose presence in the blood or cerebrospinal fluid causes constriction of arterioles, with dilatation of capillaries." And an indication of his ratiocination may be had from the following: "The vascular theory of epilepsy has appealed to me for many years as the result of a lifelong personal experience of migraine where constriction and dilatation of vessels have played a prominent part, and can, I think, throw light upon the epileptic problem."

Chapter IV on the cerebrospinal reflex in its relations to epilepsy begins with the statement "The hypothesis (sic) we advocate, that vaso-constriction is the initial movement in the epileptic seizure, without which there would be no epilepsy as we know it, may be admitted, while holding that there must be other factors in its production." And then comes the following: "Amongst the factors which must be considered as the cause of vasoconstriction are not only the toxin x, but the effects of the cerebrospinal reflex and the influence of certain glandular secretions." The burden of this chapter is a repetition of Brown-Séquard's ideas on reflex epilepsy with some rambling allusions to ideas and cases of other observers.

The next three chapters are devoted to the influence of the endocrine glands on epilepsy, traumatisms and tumors, and tuberculosis and syphilis in relation to epilepsy. They contain considerable information gathered from various sources, with running comments and a strong flavor of speculation. Here as elsewhere the case reports, while suggestive and interesting, are rather a series of memoranda than real reports.

In Chapter VIII, the author discusses what it may be in the patient or his brain that makes him have fits—and gets about as far as Hughlings Jackson did. Here again cases are sketchily introduced from which the author smugly draws conclusions satisfactory to himself.

The book shows an honesty of purpose and earnestness of endeavor wholly admirable. Obviously, the author has read widely—writings of English authors —and has pondered long and deeply. His product is easy reading and instructive. He quotes Hughlings Jackson extensively, and one cannot quote that wonderful man without quoting something worth while. The case reports are interesting, sometimes entertaining anecdotes about epilepsy, and they teach something; but of scientific research there is only a faint trace.

CRIMINOLOGY. By EDWIN H. SUTHERLAND, PH.D., Assistant Professor of Sociology, University of Illinois. Pp. 643. Philadelphia: J. B. Lippincott Company, 1924.

The general point of view which dominates this book is indicated by the author's initial definition of criminology: "Criminology is the body of knowledge regarding the social problem of crime." "Criminology is concerned with crime as a personal and group phenomenon. As such it is primarily sociological. It draws information, to be sure, from a great variety of specialized investigations — physiological, psychological, legal, chemical, economic, statistical, educational, and sociological."

The chapter headings indicate the scope of the book: I. Criminology, Law, and Crime; II. Statistics of Crime; III. The Victims of Crime; IV-VIII. Causes of Crime; IX. The Police System; X. Detention Before Trial; XI. "Popular Justice"; XII. The Court; XIII. The Juvenile Court; XIV. Origin and Evolution of Punishment; XV. Ethics and Economy of Punishment; XVI. Miscellaneous Methods of Punishment; XVII-XX. Prisons; XXI. Release from Prison; XXII. Parole; XXIII. Probation; XXIV. Methods of Reformation; XXV. Prevention of Crime.

The book presents in compact form a complete statement of our present knowledge in regard to the problem of crime. Written primarily as a textbook for students of sociology, it will be useful to all interested in this subject, not only because of the actual presentation, but also because of the bibliography which is conveniently placed at the end of each chapter.

In order to bring the material within the compass of the volume, Professor Sutherland has had to make a selection. This has been wisely done. Any one who has attempted to find his way through the mazes of the statistical publications, and especially of the older anthropologic publications in this field, will be grateful to Professor Sutherland for his excellent discrimination.

The book is written for American students of the problem and therefore confines itself in the main to a discussion of the American problems and of the American literature. It is encouraging to those who are interested in the development of this field in this country to note the growing amount of American scientific material now available.

In spite of the introductory statement quoted above, which might lead a reader to expect a rather close adherence to the purely sociological interpretation of the crime problem, a great deal of attention is paid to the factor of pathology, although this is not specifically noted throughout the book. It is interesting, for instance, that in the special headings quoted above one fails to find the words "pathologic" or "psychiatric." Nevertheless, the material presented includes a considerable amount of psychiatric and pathologic discussion.

Professor Sutherland has managed to present his subject without injecting any personal bias. The general tenor of the discussion is kept on an objective and scientific plane. Opposing theories are stated, contradictory claims are considered, and, wherever possible, evaluated with fairness. The book should prove of value to students especially, not only giving them an opportunity to acquaint themselves conveniently with the present status of the subject, but also pointing out the various problems still requiring investigation and giving some suggestions as to the methods by which further knowledge may be obtained. The book will prove of value to those who wish to inform themselves quickly on the subject and to those who are interested in the literature of criminology. The index of authors and subjects appended to the volume will further increase its usefulness as a work of reference.

This book is quite up to date, but like all such works is not apt to remain so very long. Conclusions in regard to the various topics discussed, such as causation, police, the administration of justice, the penal and correctional systems, parole, probation and prevention, are constantly undergoing modifications. It is to be hoped that the reception of this book will be sufficiently encouraging to influence the publishers to reissue it after a few years, in order to keep it abreast of future progress.

MALADIES DES NERFS PÉRIPHÉRIQUES ET DU SYMPATHIQUE. Par PITRES, Professeur a la Faculté de Médecine de Bordeaux; VAILLARD, Médecin Inspecteur Général de l'Armée, Membre de l'Académie de Médecine; LAIGNEL-LAVASTINE, Professeur Agrégé a la Faculte de Médecine de l'Hôpital Laennec. Avec 56 figures intercalées dans le texte. Pp. 857. Paris, Librairie J. B. Baillière et Fils, 1924.

This work is the thirty-sixth volume of the encyclopedic nouveau traite de médecine et de thérapeutique, edited by Gilbert and Carnot, and constitutes a full and excellent treatise on diseases of the peripheral nerves and of the sympathetic nervous system. Its only obvious defect is lack of consideration of experience gained in the Great War and in the post bellum period. The paucity of bibliographic references later than 1914 is striking. But this criticism is scarcely applicable to the section on the sympathetic (by Laignel-Lavastine) which is up to date, lucid and well balanced.

The book opens with 103 pages on anatomy, histology, physiology, degeneration and regeneration of nerves, followed by thirty-four pages of general symptomatology.

To peripheral neuritis are devoted 418 pages, and the subject is fully covered in all its aspects: mononeuritides, polyneuritides, tabetoneuritic and paretoneuritic syndromes. Korsakoff's psychosis, Landry's paralysis, ascending neuritis, hypertrophic neuritis and paralysis due to the various metallic and organic poisons, including beri-beri, all receive adequate attention.

There follow more than sixty pages on diseases of the cranial nerves, including facial hemiatrophy and facial spasm. Most of this matter is excellent, but one notes an instance of the lack mentioned above. The section of the sensory root for trifacial neuralgia is endorsed, apparently mostly on the basis of de Martel's fourteen cases without a death and with only one failure. One would think that the hundreds of cases of American surgeons might well have been considered.

Affections of the nerves of the brachial plexus, of the lumbar plexus and of the sacral plexus are well covered, the article on palsies and neuralgias of the sciatic nerve being exceptionally excellent. We do not recall reading another quite so good.

As indicated above, the section on the sympathetic nervous system (132 pages) is to be unreservedly commended.

The book might well be better illustrated, but it has a fairly good index and an excellent table of contents and will make a valuable addition to any library.

HARVARD HEALTH TALKS. A PRESENT-DAY CONCEPTION OF MENTAL DISORDERS By CHARLES MACFIE CAMPBELL, M.D., Professor of Psychiatry at Harvard University. Price, $1.00. Pp. 54. Boston: Harvard University Press, 1924.

This is one of a series of Harvard Health Talks for the laity and is a delightfully written essay on the mechanisms of behavior, normal and abnormal. Without doubt it will carry illumination to every layman concerning the cause of certain actions and certain personalities, and we believe that many physicians would profit richly by reading it two or three times.

The author starts by indicating that many every-day types of character, emancipated, eccentric, model, are really mental disorders. He asks a series of questions like the following: "Can the blameless and model individual, following smugly in the parental footsteps, be the victim of a disorder consisting essentially in the repression of the most productive elements in the individual's nature?" But why he puts these statements in the form of questions is not entirely clear. He then pleads that the same consideration be given to emotional states as is currently given to teeth and blood pressure.

From the simply exceptional or only annoying things, the author passes to the frankly pathologic and stresses the point that mental disorder is the result of "human nature working under difficulties." In pursuing this thesis, his reasoning is clear and his illustrations apt, and the entire exposition excellent, even masterly.

We have no reason to doubt the ability of the audience to which this lecture was delivered instantly to appropriate it, promptly to digest it and completely to assimilate it, but we are constrained to believe that few lay audiences outside the precincts of Boston could show equal gastronomic ability. Attainments lower than those of a Harvard senior would not permit immediate assimilation. Hence the foregoing suggestion that many physicians should read it several times.

INFANTILE PARALYSIS IN VERMONT, 1894-1922. A MEMORIAL TO CHARLES S. CAVERLY, M.D. Pp. 375. Burlington, Vermont: State Department of Public Health, 1924.

This book is pleasing evidence that official bodies are not always soulless. It is published by the State Department of Public Health of Vermont and "has been prepared as a memorial to Dr. Charles S. Caverly. It consists, in the main, of his writings on the subject of poliomyelitis in Vermont, to which are added certain contributions from the men who worked with him or after him, and a statement of the present status of the work instituted by him."

The introduction states that "The history of infantile paralysis in Vermont really falls into three divisions: (1) the epidemiologic study of the disease; (2) the treatment of affected cases; and (3) the work of the research department," and these three subjects are excellently well covered in papers by Dr. Caverly, by Dr. R. W. Lovett of Boston and his co-workers and by six papers from the research department of the State Department of Public Health by Drs. Aycock, Amoss and Taylor working under the direction of Dr. Flexner of the Rockefeller foundation.

These papers are preceded by a brief sketch and appreciation of Dr. Caverly by Dr. Lovett. Evidently, Dr. Caverly was a great and good man, and this book is not only a graceful tribute to his usefulness and character, but also a valuable contribution to the archives of poliomyelitis.